ANNALS OF
INTERNAL MEDICINE

VOLUME 48 MAY, 1958 NUMBER 5

CARCINOMA OF THE STOMACH *

By CHARLES A. FLOOD, M.D., F.A.C.P., *New York, N. Y.*

THE initial recognition of carcinoma of the stomach is usually the function of the family physician or internist. Individuals who suffer from upper gastrointestinal symptoms compose a large group of those patients who seek medical attention. Many of these patients suffer from complaints which suggest the possibility of carcinoma of the stomach. The family physician or internist is usually in the position of being the first to consider this diagnostic possibility. It is likewise often his responsibility to decide when the diagnosis of cancer can safely be excluded from consideration as the explanation of digestive symptoms.

The treatment of carcinoma of the stomach belongs chiefly in the domain of the surgeon. However, problems which are related to the pathogenesis and diagnosis of carcinoma of the stomach are equally important to the internist and surgeon. The present review is an attempt to summarize various aspects of the problem of carcinoma of the stomach which concern the internist. Current investigations which relate to etiology, questions of differential diagnosis and various disorders which arise after definitive surgery are emphasized.

ETIOLOGY

Little is known concerning the etiology of gastric carcinoma. A large body of data has nevertheless been accumulated which suggests that both hereditary and environmental factors exercise a significant rôle. The validity of some of these observations is open to some question because many of them are based upon vital statistics where the possibility of error may be

* Received for publication November 19, 1957.
From the Department of Medicine, The College of Physicians and Surgeons, Columbia University, and The Presbyterian Hospital, New York.
Requests for reprints should be addressed to Charles A. Flood, M.D., Harkness Pavilion, 180 Fort Washington Avenue, New York 32, N. Y.

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rather large. This is particularly true of many but not all reports of variations in geographic distribution.

Carcinoma of the stomach exhibits a definite familial trend. It occurs about four times as frequently among the relatives of patients with gastric carcinoma as would be expected on the basis of chance distribution.[1] Studies have also shown that the children of patients with gastric cancer are destined to develop the disease in numbers which are greatly in excess of chance expectancy. The importance of heredity as an etiologic factor is also supported by the observation that gastric carcinoma occurs occasionally in identical twins.

Recent studies which have correlated carcinoma of the stomach with blood Group A also suggest that hereditary factors play an etiologic rôle. A slight preponderance in the incidence of gastric cancer among persons

TABLE 1

Mortality from Cancer of the Stomach in Different Countries

Country	Period	"Average" Death Rate per 100,000 Men (ages 35–74)	Female Rate as Per Cent of Male
Japan	1951	220	51%
Finland	1951–3	216	56%
Iceland	1940–9	209	62%
Norway	1952	131	51%
Netherlands	1950–2	116	60%
Denmark	1951–2	96	58%
France	1952	94	54%
England and Wales	1951	91	53%
Sweden	1952	90	66%
Israel	1951	86	67%
U. S. A. (nonwhites)	1952	76	43%
Canada	1950	75	51%
Venezuela	1950	65	67%
U. S. A. (whites)	1952	48	50%

having blood Group A has been recorded in England.[2] A similar association between cancer of the stomach and blood Group A has been noted in several other countries. However, although this relation was found in the United States, it was less striking.[3] In Australia a significant preponderance of cancer of the prepyloric and cardiac portions of the stomach was found in individuals with blood Group A, but the relationship did not apply to patients with cancer in the midportion of the stomach.[4] At present it appears that there is a greater tendency for carcinoma of the stomach to occur among individuals with blood Group A than with other blood groups.[5] The differences are numerically small but seem to be significant.

Heredity is of great importance in experimental studies on the production of carcinoma of the stomach in the mouse. Strong in 1945, using methylcholanthrene as a carcinogenic agent, was able to induce a malignant tend-

ency in hybridized mice which tends to be transmitted to succeeding generations without further administration of the drug.[6]

Environment may also play an important rôle in pathogenesis. The possible importance of environmental factors in the etiology of gastric cancer is suggested by observations on the differences in the incidence of the disease in different localities. Conclusions concerning geographic distribution must be interpreted with caution, since most of the studies are based on vital statistics. However, the data are provocative because wide differences exist in the reported incidence of gastric cancer in the various countries of the world. Recent figures compiled by Doll are illustrative (table 1).

It appears that such differences in geographic distribution are related more to environmental factors than to racial predisposition. Marked differences in incidence are recorded for countries in which the racial groups are relatively comparable, and the highest rates are found in countries with very different racial stocks. The incidence of gastric cancer also may vary considerably within the confines of a single country.

In the United States the average death rate from cancer of the stomach for white males between 35 and 74 years of age has recently been reported to be 48 per 100,000. In Japan the death rate from cancer of the stomach is five times as great as among whites in the United States.[8] In fact, it appears to be well established that cancer of the stomach is more common in Japan than in any other country. A high rate among the Japanese is also said to occur in reports from the Hawaiian Islands. In this locality, cancer of the stomach is twice as common among the inhabitants of Japanese ancestry as among the Caucasian population.[9]

In Finland, Iceland and Norway the incidence of gastric cancer is high and approaches the level reported in Japan.[10, 11] Canada and the United States have the lowest incidence of cancer among the countries from which detailed statistical data are available. Thus, in the Province of Saskatchewan, careful studies revealed an incidence in males over 35 years which ranged from 41.4 to 66.8 per 100,000 during the period 1945 to 1952, a rate comparable to that found in the United States.[12] Incidences of intermediate magnitude are recorded in the western European countries and in England and Wales.

Racial susceptibility will not explain the reported variations in the distribution of the disease in different countries. High rates of comparable magnitude are found in Japan and in some of the Scandinavian countries. Wide differences in incidence are reported from countries in which the majority of the population is white.

Although racial factors fail to explain some of the variations in incidence, there are examples of racial differences in the incidence of carcinoma of the stomach within single countries. The incidence of gastric cancer in the United States, for example, is greater among the nonwhites than among

whites. In Sumatra, gastric cancer has been reported to be rare among the Javanese but common among the Chinese.

Several recent reports suggest that the incidence of gastric cancer varies according to the type of soil in different localities. In Holland, for example, higher frequencies have been observed in communities located on heavy sea clay soils than in communities situated on light sea clays or river clays.[13] In Wales, higher frequencies of gastric cancer are reported in poorly drained areas which are rich in peat or other organic substrata.[14]

Statistical methods of study have led to a number of other conclusions concerning the significance of other environmental factors. No apparent relationship exists between the occurrence of gastric cancer and the use of alcohol and tobacco. Occupation does not seem to play a rôle. There seems to be some relationship between gastric cancer and social status. In England and Wales the disease is reported to be over twice as common in poorer income groups as in the wealthy. In recent years the frequency of gastric cancer has declined slightly in a number of countries, including the United States. However, the explanation for this probable trend is uncertain.[15]

Animal experimentation has yielded observations which may have important significance in the understanding of the pathogenesis of human cancer. Malignant tumors have been produced in the glandular portion of the stomach of rats and mice when carcinogenic hydrocarbons are embedded in the stomach wall. Such tumors have been produced only when the carcinogenic hydrocarbon is introduced into the stomach wall, and do not occur as a result of simple mucosal contact alone with the carcinogenic substance. The intramural injection of methylcholanthrene into the stomach of the rat results in the production of malignant tumors.[16] Such lesions have also been produced in the rat by the ingenious method of introducing methylcholanthrene into the gastric wall by means of impregnated suture material, a procedure which allows the carcinogen to remain in prolonged contact with the deeper tissues.[17] The feeding of carcinogenic hydrocarbons has failed to cause the formation of malignant tumors in the glandular portion of the stomach. These observations seem to indicate that the carcinogen is unable to penetrate the mucosal surface of the stomach. That hydrocarbons are not water soluble may be an important factor. The possibility has also been suggested that a stomach which has previously been subjected to mucosal injury might be more readily susceptible to a carcinogenic agent.[18]

Attempts have been made to relate the ingestion of superheated fats in the diet to carcinogenesis. Overheated fat has been shown to contain a low grade carcinogen which is active when given subcutaneously to rats.[19] It produces various types of benign and malignant tumors. The feeding of overheated fat to mice has been reported to result in the development of carcinoma of the stomach, according to some workers, but others have failed to confirm these results.

Premalignant Conditions of the Stomach

It has been hypothesized that a previous injury to the stomach is essential for the development of gastric carcinoma. Konjetzny provided extensive pathologic documentation to support the view that cancer does not develop in a previously normal stomach. This observer noted chronic inflammatory changes on histologic study in a large proportion of individuals with gastric carcinoma.[20] Others have questioned the significance of such observations. It is pointed out, for example, that inflammatory changes, mucosal atrophy and metaplasia occur in the gastric mucosa with increasing frequency in the later decades of life. It is difficult to be sure, when such changes coexist with cancer of the stomach, that the association is a significant one.

Nevertheless, a number of observations may be interpreted to support the concept that preëxisting mucosal injury favors the development of gastric cancer. The argument is supported by studies which correlate the incidence of gastric cancer with achlorhydria, mucosal atrophy, pernicious anemia, benign adenomata and benign peptic ulcer.

Achlorhydria is a finding in over 50% of patients found to have gastric carcinoma. In one study of patients with gastric carcinoma the secretion of hydrochloric acid was found to be impaired before carcinoma became manifest in a higher proportion of individuals than could be attributed to the aging process alone. Comfort et al. carried out a retrospective analysis of the results of gastric analysis using the Ewald meal in a group of patients who developed clinical evidence of gastric carcinoma two or more years later.[21] Achlorhydria had been present on the initial gastric analysis in 47.8% of patients, a figure that is unusually high even in the older age groups. The incidence of achlorhydria later rose to 68.8% at the time of the diagnosis of cancer. Evidently the secretion of hydrochloric acid was abnormal in a disproportionately high number of individuals in this group even prior to the development of cancer.

The rather high incidence of carcinoma which develops in patients with pernicious anemia may also be interpreted to indicate that a mucosal abnormality or mucosal injury, in the broader sense, precedes the development of carcinoma. Mucosal atrophy and achlorhydria in patients with pernicious anemia are usually observed to be present prior to the appearance of neoplasm. It is now well established statistically that gastric cancer develops in individuals with pernicious anemia at approximately three times the rate in control groups.[22, 23, 24, 25] The sequential relation of mucosal atrophy and cancer in pernicious anemia appears to be well established. The exact significance of this relationship has not been established. It has been shown that cancer of the stomach is three times as common among the relatives of patients with pernicious anemia as would be expected from chance distribution. It is possible, therefore, that there is an inherited defect which affects the gastric mucosa in the families of patients with pernicious anemia.[26]

Adenomatous polyps of the stomach are usually regarded as precursors of gastric carcinoma. Polyps are of particular interest in the study of the pathogenesis of cancer for two reasons: they occur chiefly in stomachs which exhibit mucosal atrophy, and there is considerable evidence that they may be premalignant lesions.

Gastric polyps are found very frequently in patients with pernicious anemia. They are usually too small to be detected by radiologic technics, and are found much more often by means of gastroscopic examination. Gastroscopic studies reveal polyps in 5 to 10% of individuals with this disease.[27, 28] The association of mucosal atrophy and polyp formation is also found in individuals without pernicious anemia. The majority of adenomatous polyps occur in stomachs with evidence of atrophy in patients who have no other disease.

Microscopic studies of polypi suggest that malignant transformation is frequent.[29, 30] There are also reports in the literature of patients with radiologic evidence of a small polyp which was initially treated conservatively and which proved to be malignant after a period of years.

The malignant potentiality of benign adenomata has been questioned by Carey.[31] A long-term study of patients with polypi was carried out in which the patients were subjected to periodic gastroscopic examination. This inspection of gastric polyps suggested that malignant polyps are probably malignant from the beginning, and that benign polyps remain benign. It was possible to classify most of the benign polyps on the basis of gross appearance. Lesions which were benign usually appeared as smooth-domed protrusions from the mucosa, or as small, elongated tumors on a stalk. Tumors of this type, which were considered to be benign initially, were never observed to undergo malignant changes over a follow-up period of from five to 10 years. Malignancy in polyps, on the other hand, may be suspected on the basis of other gross findings, such as ulceration or irregularity on the mucosal surface. In this study, when the gross changes were suggestive of malignancy, such changes were present on initial examination.

The question of malignant transformation of benign polyps remains a controversial one, and the problem manifestly is a difficult one to resolve. In the course of these investigations it has been clearly established that adenomata occur chiefly in stomachs which show atrophic changes. It seems well established that both adenomata and carcinoma occur more often in the stomach which is otherwise diseased than in the stomach which seems to be otherwise relatively normal.

The possibility that gastric ulcer is a premalignant lesion has been subjected to extensive investigation. Wilson and McCarty in 1909, on the basis of pathologic studies of resected stomachs, suggested that malignant changes occurred in approximately two thirds of gastric ulcers.[32] Many pathologists have subsequently studied this question, and the estimates of

the number of benign ulcers associated with malignancy have been much lower than was suggested earlier.[33-40] Recent studies based upon interpretation of histologic findings suggest that from 5 to 15% of gastric ulcers are associated with malignancy. It is noteworthy that a higher incidence is reported in surgically removed specimens than in autopsy material. This is attributable to case selection. Many patients who are subjected to surgery have presented evidence of an ulcer in which malignancy is suspected because of resistance to medical treatment.

Pathologic appraisal of the possible relationship between cancer and ulcer depends chiefly on the evidence obtained by studies made at the time of operation or autopsy. Additional data concerning this question have been supplied by clinical observation. Long-term observation of patients with gastric ulcer affords some support for the hypothesis that there is an increased tendency toward development of carcinoma in the stomachs affected by benign ulcer.

Patients who have a carcinoma which appears at the time of operation to have arisen on the basis of a preceding benign ulcer often have a clinical story which suggests a previous ulcer. Approximately one-half of such patients give a long history of gastric symptoms.

Long-term follow-up observation of a series of patients who initially presented evidence of a benign gastric ulcer by the usual criteria reveals that cancer develops in a small number of individuals.[41] In a series of 101 patients with gastric ulcer who were followed for an average period of 5.6 years, cancer developed in five patients after intervals which varied from three to 18 years. The carcinoma seemed to have arisen approximately in the site of the previous ulcer in three instances. It probably arose in a site which was distant from the ulcer in the other two cases.

Other observers maintain that the occurrence of cancer of the stomach in individuals who have previously had a gastric ulcer is fortuitous. It has not been proved that this sequence of events takes place more often than can be explained on the basis of chance alone. Moreover, it may be argued that ulcers which seem benign by all of the usual clinical and laboratory criteria and subsequently are found to harbor malignancy when the ulcer recurs at some future date are in fact examples of slowly developing carcinomata which have been present from the onset. The fact that gastric carcinoma may at times require many years to evolve seems to be clearly established. Occasional examples of very slow-growing gastric carcinomas which have been known to be present for a number of years have been documented in the literature.[42]

Cancer Detection Surveys

The disappointing results in the treatment of gastric cancer after it has become clinically manifest have led to efforts to detect the lesion at an earlier and silent stage. This has been effected by means of radiologic surveys

of asymptomatic individuals in the appropriate age groups. This type of study is laborious, and a large number of people must be surveyed in order to discover one patient with malignant disease. Recently, practical advantage has been taken of the fact that a number of gastric disorders can be regarded as premalignant, and the survey technics have been oriented toward the study of more highly selected groups of patients.

The first attempt to survey the population for silent gastric carcinoma was reported in 1944 and covered a relatively unselected series of people over 50 years of age. St. John et al. studied by rapid fluoroscopy 2,400 individuals who were free from gastric symptoms and encountered three malignant gastric tumors.[43] Other surveys using fluoroscopy or photofluorometric technics have shown a comparable incidence of cancer in the older age groups.[44, 45, 46]

The fact that surveys of the general population for silent gastric carcinoma yield a low percentage of cases is in accord with the view that the length of time during which gastric carcinoma is clinically silent is usually rather short. General clinical experience suggests that the silent period of gastric cancer is of short duration. Autopsy observations likewise suggest that the silent period of most cases of gastric cancer is not a long one. Asymptomatic gastric carcinoma is an infrequent incidental finding at the autopsy table.[47]

With a low yield in the detection of silent gastric carcinoma in the general population, survey programs have been concentrated on groups of patients who are classified as having potentially precancerous gastric disorders. As would be anticipated, the number of silent cases of cancer revealed by this approach has increased. At the University of Minnesota 1,769 individuals in the older age groups with achlorhydria or hypochlorhydria (free hydrochloric acid below 30°) were studied at yearly intervals over a nine and one half year period. Nineteen gastric cancers were encountered in this group. This incidence was estimated to be 7.1 times the expected rate for people in the same age group.[48]

The introduction of tubeless gastric analysis has recently provided a new method for the detection of achlorhydria in large groups of individuals.[49] Gastric analysis performed with the azure A resin compound has been shown to be a satisfactory method for the detection of achlorhydria. It avoids the discomfort of the standard method of gastric analysis, and provides a useful screening technic for the selection of individuals for group survey.

Patients with pernicious anemia form a special group who may be subjected to periodic survey for the development of gastric malignancy. Annual or biannual radiologic examinations have been recommended by various workers.[27, 50] Periodic gastroscopic and cytologic examinations have also been advised. However, these procedures may be impractical in individual instances. Furthermore, it must be admitted that, although the incidence of gastric cancer in people with pernicious anemia is statistically greater

than that in the general population, the per annum risk rate of the development of cancer is small.

Diagnosis

In most cases the diagnosis of gastric cancer is based upon an appraisal of the clinical picture and a demonstration of an abnormality in the stomach by means of the x-ray. Early recognition of cancer after it becomes symptomatic is possible in most instances through a proper evaluation of symptoms and competent radiologic study.

Symptoms: The first clinical manifestations of gastric carcinoma are varied. There is no single symptom complex which may be said to characterize the early clinical picture of the disease. In the majority of patients the initial symptoms are very mild and the patient is prone to disregard them. In over one third of patients the time interval between onset of symptoms and establishment of diagnosis is more than one year.[51] Delays in diagnosis are attributable both to failure on the part of the patient to seek medical advice and to failure on the part of the physician to establish the correct diagnosis.

The symptoms of gastric carcinoma are not infrequently attributed to emotional causes. In individual instances a tendency to attribute gastric symptoms to anxiety may lead to delay in seeking medical attention or in carrying out the appropriate medical work-up.

Upper abdominal discomfort is the most common first symptom of cancer of the stomach. This distress may be characterized by the patient variously as fulness, burning or indigestion. It may resemble the pain of peptic ulcer. The patient frequently finds it difficult to describe the exact character of the distress. It may or may not be related to food intake. The intimate mechanism of these symptoms is poorly understood.

Obstructive symptoms may appear relatively early if the tumor is at or near the cardia or in the distal antrum. Symptoms of anemia occasionally are part of the early clinical picture, but gross hemorrhage is an uncommon early symptom. Acute perforation is likewise rather rare, but also occurs occasionally during the early clinical phase of the disease.

Constitutional symptoms, including fatigue, weight loss and anorexia, unaccompanied by any symptoms which refer directly to the gastrointestinal tract, are the initial complaints in a small proportion of patients with gastric carcinoma.

Laboratory Procedures

Several simple laboratory procedures are helpful, although of limited value in diagnosis. Persistently positive tests for occult blood in the stool may be encountered. Absence of secretion of free hydrochloric acid in response to histamine stimulation occurs in somewhat over 50% of patients with gastric cancer. Gastric analysis is helpful if achlorhydria is demon-

strated, but the procedure is essentially of no assistance in diagnosis if free acid is found to be present in the gastric contents.

Recently, estimation of the peptic activity which is present in the urine has been a subject of investigation.[52] The results of this determination in patients with gastric disorders are of interest. The peptic activity of the urine, uropepsin, is reduced in many patients with gastric carcinoma. This observation reflects the reduction in gastric secretion of pepsin usually noted in the disease. According to Gray and others,[53] low uropepsin values favor a diagnosis of gastric malignancy. Values of less than 1,000 units were encountered in 55% of a group of patients with cancer, as compared with 1.1% of patients with gastric ulcer. Others have reported that uropepsin determinations are of limited usefulness as an aid in differential diagnosis.[54]

Radiologic Examination: Use and Limitations

Radiologic examination is the chief method for the establishment of the clinical diagnosis of gastric cancer. This procedure should be carried out on any individual who suffers from upper abdominal symptoms of more than one or two weeks' duration if the cause for the symptoms is not readily apparent.

For practical purposes, the results of radiologic examination fall into three main categories. Some x-ray findings may be classified as being pathognomonic or highly suggestive of cancer. Other radiologic findings are consistent with malignant disease but may also occur in various benign disorders. Third, the radiologic examination is essentially negative in some patients with carcinoma.

The presence of a filling defect on x-ray examination is usually reliable evidence of a space-occupying lesion in the gastric wall. As a rule, this finding constitutes convincing proof of the presence of a neoplasm. X-ray evidence of irregular mucosal destruction in the stomach is also strong evidence of malignancy. This radiologic sign is found with malignant infiltration of the gastric wall. Such radiologic findings are generally sufficient to justify a clinical diagnosis of cancer and usually provide information which determines the proper course of therapy, regardless of other clinical data.

A number of other radiologic signs may suggest the possibility of cancer. Among these are ulcer craters, relative loss of distensibility of the gastric wall, narrowing of the antrum or, at times, wide, irregular mucosal folds. Such changes are usually also consistent with benign disease. In fact, the demonstration by x-ray of any lesion in the stomach raises a question of cancer as a general rule. The problems in differential diagnosis which arise when radiologic study reveals evidence of a lesion which could be either benign or malignant will be discussed separately.

Radiologic examination reveals some abnormality in a high percentage of patients with cancer. Statistically speaking, the method is very dependable as a means of detecting the presence of a carcinomatous lesion, and it

is a very effective screening procedure. Failure to demonstrate a lesion is generally accepted as strong evidence that no carcinoma is present.

Precise data which would permit an estimate of the over-all accuracy of the x-ray method in the detection of gastric cancer are impossible to secure because of the fact that those instances in which the examination has failed to demonstrate a lesion may remain unknown to the examiner. However, numerous reports from large hospitals of series of patients with gastric cancer show that radiologic examination reveals the presence of a lesion in approximately 95% of patients who are found to have gastric carcinoma (Abrahamson and Hinton, 95%;[55] Maimon and Palmer, 100%;[56] Cooper, 96.6%;[57] Engel, 82%;[58] Miller, 97.5%;[59] Anglem, 94.8%[60]). The high degree of diagnostic accuracy reported from large hospitals may be attributable to some extent to the case selection which occurs in the referral and admission of patients to such institutions.

The results of x-ray examination of ambulatory patients are evidently somewhat less reliable. Templeton has recently evaluated the accuracy of the x-ray method in the office practice of radiology.[61] In this author's study all of the examinations were carried out by experienced radiologists. In the hands of these examiners the over-all accuracy in demonstration of a lesion in patients later shown to have gastric cancer was 88%. Detailed analysis showed that errors were attributable to many factors, including divided attention of the examiner, poor technics, overcalling and misrepresentation of the evidence, and failure to repeat the examination when there were dubious findings.

A second x-ray study may be of great value for better definition of a problem when the first examination has revealed the presence of a gastric lesion. In a series of patients who had gastric cancer, Cooper found that the initial x-ray examination resulted in a definite diagnosis of carcinoma in 70.7% of cases. The stomach appeared normal in 4% at the time of the first study. A lesion of indeterminate nature was demonstrated in the remaining individuals. After repeated x-ray studies the incidence of positive diagnosis of cancer in this series rose to 86% and the number of negative examinations fell to 2.2%.[57]

Cancer may be present in any part of the stomach but fail to be demonstrated by radiologic examination.[34] Lesions of the fundus may be particularly difficult to identify because the rib margins interfere with palpation by the radiologist. Any morphologic type of gastric carcinoma may fail to be demonstrated. The largest proportion of lesions not seen by x-ray are of the infiltrating type. Ulcerating and polypoid carcinomata and linitis plastica are also occasionally present in patients with normal appearing x-rays.

Gastroscopic Examination

Gastroscopic examination and cytologic study of the gastric contents are the other chief methods for the establishment of the diagnosis of gastric

cancer. Their practical usefulness lies chiefly in the study of individuals with x-ray evidence of disease of the stomach the exact nature of which is indeterminate. Both methods have the disadvantage of being disagreeable procedures for the patient.

The findings on gastroscopic examination in patients with carcinoma of the stomach may also be divided into three categories: there may be practically unequivocal evidence of malignancy, there may be a lesion which appears to be benign or indeterminate, or the examination may be entirely negative.

Cancer of the stomach may appear gastroscopically as a massive lesion protruding into the lumen, or it may be seen as a nodular, necrotic or irregularly ulcerative process in the gastric wall. Such findings are virtually pathognomonic of the disease. Other gastroscopic changes found in patients with carcinoma have an appearance which is less diagnostic of malignancy and may be confused with benign lesions. Thus, a malignant ulcer with swollen and irregular margins may present an appearance indistinguishable from that presented by a severely inflamed benign ulcer. At times a malignant ulcer may seem to be entirely benign in its gastroscopic appearance. Infiltrating carcinoma may result in wide nodular mucosal folds which, when viewed gastroscopically, resemble the gross picture of so-called "hypertrophic gastritis."

The over-all accuracy of the gastroscopic diagnosis of cancer averages about 77% in the hands of experienced gastroscopists.[62] The most common source of error is failure to visualize the lesion. Portions of the antrum and posterior wall of the stomach usually remain out of view during the examination, and lesions in these locations may be inaccessible. Attempts have been made to overcome this difficulty by the use of a gastroscope of the Taylor type, so constructed as to enable the examiner to bend the lower end of the instrument in various directions and thereby to visualize portions of the so-called "blind areas." [63]

Errors in interpretation of gastroscopic findings are also rather common. The erroneous suspicion of the presence of malignancy in a benign lesion is a more common error than is failure to recognize the possibility of carcinoma when present.

Biopsy obtained during gastroscopy has proved to be useful in the resolution of some of the diagnostic problems, especially if the suspected lesion is rather diffuse.[64] If a diffusely abnormal area is encountered at gastroscopy, a biopsy may be taken through the operating gastroscope for the establishment of a tissue diagnosis. Small localized lesions are technically difficult to biopsy, and it is often impossible to obtain a satisfactory specimen of tissue; hence the biopsy technic has not proved to be very useful in the study of such lesions as peptic ulcer and small polyps.

The most useful application of the gastroscopic method is in the study of lesions demonstrated by x-ray in which the diagnosis is in doubt. Gastro-

scopic examination may be helpful in determining whether early surgery should be advised. A series of patients with indeterminate x-ray findings due to carcinoma of the stomach was reported by Moersch and Kirklin.[65] The results of gastroscopy in this group of patients were positive for cancer in 90% and indeterminate in 10%.

The over-all accuracy of the diagnosis of gastric cancer is improved when the results of radiologic and gastroscopic examinations are appraised together. In one series of patients who were shown to have carcinoma the x-ray diagnosis alone was considered to be correct in 73%. The two methods in combination resulted in a diagnostic accuracy of 91.5%.[66]

Cytologic Diagnosis

A method for the detection of cancer cells in gastric washings was introduced in 1947 by Cooper and Papanicolaou.[67] The method consisted of gastric lavage, after appropriate preparation of the patient, and microscopic study of the sediment for the presence of malignant cells. Subsequently a number of modifications in procedure have been proposed. Mechanical abrasion of the gastric mucosa has been used in an effort to obtain better cellular material for histologic study. This may be done by means of a condom balloon which is surrounded by a coarse veiling or with a brush which is attached to the end of a tube. Enzymes such as chymotrypsin have been added to the lavage fluid for the purpose of clearing the specimen.[68-72]

It appears that the factors of greatest importance in increasing the reliability of cytologic diagnosis are the care exercised in obtaining material, and competent evaluation of the histologic preparations. Preliminary removal of all debris from the lumen of the stomach is essential. This may be difficult if there is pyloric obstruction. After the gastric contents have been aspirated, rapid fixation is essential in order to secure good cellular preservation. The procedure of scanning the prepared slides for cancer cells requires expert interpretation and is time-consuming.

Cytodiagnosis has attained a rather high degree of reliability as a method for the diagnosis of gastric carcinoma. A number of authors have reported an over-all accuracy of approximately 80%.[69-72] Comparable degrees of accuracy appear to be attainable through the use of a number of technics. Minor differences in method do not appear to influence the accuracy of the procedure to any major extent.

False-positive reports of gastric malignancy are quite infrequent, according to experienced workers. In one collection[71] of 313 patients, only four such reports were recorded. Moreover, the procedure of cytodiagnosis has been shown to be of value in the detection of early lesions of the stomach. Patients with a small carcinoma such as a carcinoma in situ have now been observed in whom a positive diagnosis was established by means of cytodiagnosis. Nevertheless, the procedure is not as yet a fully established

one. A number of disappointing reports on the accuracy of cytodiagnosis are contained in the literature.

Electrogastrogram

The use of the electrogastrogram as a clinical diagnostic aid was suggested by Goodman in 1942. The procedure involves gastric intubation and a suitable apparatus for recording differences in electrical potential between the gastric mucosa and the skin. The normal stomach has a characteristic pattern of electrical behavior.

Studies to date indicate that marked deviations from normal occur in many individuals with gastric carcinoma. In a large series of patients with benign or malignant disease of the stomach the electrogastrographic findings were correct in two thirds of the cases.[73] It appears that the electrogastrogram has limited application to problems in diagnosis.

Differential Diagnosis: Lesser Curvature Ulcer

Problems in the differential diagnosis between benign gastric disorders and carcinoma are numerous. A number of radiologic findings are compatible either with a benign process or with cancer. It is true that the proportion of patients with carcinoma who have x-ray findings not strongly suggestive of malignancy is relatively small. Only about 20 to 25% of patients with gastric cancer present such difficulty in differential diagnosis. However, it is essential to consider the possibility of cancer in the evaluation of patients who prove to have benign lesions and, as a result, problems in differential diagnosis are very common. The most common disorders of this type are benign peptic ulcer and benign antral disease. Another less common problem of the same type is that of the patient in whom the radiologic demonstration of wide mucosal folds raises the question of malignancy.

The finding of an ulcer crater in any portion of the stomach always poses a problem in differential diagnosis. In order to consider the problem, it is advantageous to classify separately ulcer craters found by x-ray examination in the body of the stomach at or near the lesser curvature from craters situated in the antrum or on the greater curvature. The former type, ulcer craters located on or near the vertical portion of the lesser curvature proximal to the incisura angularis, proves to be malignant in 10 to 20% of patients who present this finding.[74]

A number of radiologic signs may be of assistance in the differential diagnosis of such lesions. If the niche projects well beyond the contour of the lesser curvature of the stomach the lesion is probably benign. Radiation of mucosal folds in stellate fashion out from the crater shadow favors a benign process but does not guarantee it. Crater shadows which do not project beyond the general contour of the lesser curvature are suggestive of malignancy. When a crater shadow presents a concave surface facing

the gastric lumen (meniscus sign), the possibility of malignancy is strongly suggested. Irregularities in the margins of a crater shadow are signs which are likewise suggestive of a malignant process. Very large crater shadows (more than 2.5 cm. in diameter) are more often due to a malignant than to a benign process.

Exceptions to all of these x-ray criteria for benign or malignant ulcer may be encountered. At times crater shadows which seem typically benign by the usual criteria prove to be due to malignant disease. The criteria for malignant ulcer craters are also subject to error. A single x-ray examination cannot be fully relied upon for definitive diagnosis in this type of problem. Additional studies are usually indicated to aid in the decision as to appropriate management.

Gastric analysis using histamine stimulation should be performed routinely. If an absence of free hydrochloric acid is reliably documented, it may be assumed that the lesion is a malignant one, in view of the constancy with which free acid is secreted by patients with benign peptic ulcer. Examples of benign ulcer have only occasionally been recorded in which the gastric analysis revealed no free hydrochloric acid. Under these circumstances repetition of the test using maximal histamine stimulation and x-ray verification of the position of the stomach tube usually yields free acid and indicates that the original observation was not technically valid. Instances of benign peptic ulcer in which gastric analysis has reliably demonstrated a transitory achlorhydria have only rarely been encountered.[75]

The most useful method for differential diagnosis of crater shadows in the upper two thirds of the stomach is that of serial x-ray examinations performed during an intensive trial of ulcer therapy with observation of the rate and extent of healing. Such a program entails repeated radiologic studies until complete healing has been demonstrated. The second x-ray examination should be performed after approximately three weeks of therapy. If at that time the crater shadow has decreased in width to between a third and a half of the initial size, the response to treatment is regarded as satisfactory and the diagnosis of a benign ulcer is favored. This type of response is noted much more frequently with benign than with malignant lesions, although malignant ulcers occasionally decrease in size under observation. Such a decrease in crater size occurring in patients with malignancy can be due to growth of the tumor and consequent filling in of the crater with neoplastic tissue.[76] If this occurs, other radiologic findings will probably reveal the true nature of the process. Malignant ulcers are apt to be marked by irregularity or rigidity of the stomach wall. Restitution of the stomach shadow to normal does not occur.

If satisfactory evidence of healing is found after three weeks, medical therapy may be continued and further radiologic studies done at intervals until all evidence of a lesion has vanished and the appearance of the stomach has returned to normal. Under such conditions the ulcer may be regarded

as benign. Only rare instances have been recorded in which all radiologic abnormalities have disappeared and the ulcer has later been demonstrated to be carcinomatous.

The average healing time of a benign ulcer crater is about six to eight weeks after the initiation of conservative treatment. However, variations in rate of healing are wide. Some craters vanish within two weeks, while other benign lesions have been observed to persist for more than three months in patients who meanwhile have refused surgical intervention. The size of the ulcer crater is not always a major determining factor in healing time. Some large craters may disappear with striking rapidity while, in some instances, small benign ulcers may heal very slowly.

The test of healing is very reliable as a method for the detection of malignant ulcer, but it is unfortunately of limited value in the diagnosis of benign ulcer. A sizable proportion of benign ulcers fail to show satisfactory evidence of healing in terms of the criteria which have been mentioned. In one series of 228 patients with ulcers in various locations, 27 individuals underwent subtotal resection because of lack of response to medical management.[77]

At gastroscopy a typical benign ulcer appears as an oval crater with a clean white base and smooth, sharply demarcated margins. Malignant ulcers often have an irregular contour, with margins which are either nodular or ill defined, and a necrotic base which appears to be discolored. Sometimes benign ulcers present gross characteristics which arouse a suspicion of malignancy. Findings such as nodularity of the margin of the ulcer, or elevation of the entire lesion with protrusion into the gastric lumen, may falsely suggest neoplasm. The over-all diagnostic accuracy of gastroscopy in the diagnosis of benign or malignant ulcer which can be visualized at the time of study is approximately 85 to 90%.

In the management of patients with x-ray evidence of a gastric ulcer, opinion is somewhat divided concerning the advisability of attempting to establish a diagnosis by conservative means as opposed to early surgical intervention. Early surgical intervention is favored by those who point to the small operative risk which now exists for subtotal gastrectomy for benign ulcer, and to the fact that surgery offers a prompt resolution of the diagnostic problem and is an excellent treatment for benign as well as malignant lesions. Current technics for biopsy of a suspicious ulcer and quick frozen section now facilitate diagnosis in the operating room and adoption of the appropriate operative procedure. Moreover, a delay of a number of weeks for trial of conservative therapy might allow the disease, if it happens to be cancer, to spread or metastasize during the waiting period and so become inoperable. Some evidence is available which suggests that the cure rate for carcinomatous ulcer which resembles peptic ulcer is considerably higher than that for carcinoma of the stomach in general, a claim which lends some support to a policy of surgical intervention without much delay.[78]

If a conservative approach to the problem of diagnosis of ulcer is elected, lesions in the vertical portion of the lesser curvature or on the adjacent anterior or posterior walls can usually be evaluated adequately by means of serial radiologic examination during ulcer therapy, gastric analysis and, if feasible, gastroscopy or cytologic study of the gastric contents. In the event of continuing doubt as to diagnosis after a period of observation and study, surgical intervention will usually be indicated. In many cases the estimated risk of surgery is the most important factor which determines the type of management.

Benign and Malignant Disease of the Antrum

The management of patients with x-ray evidence of abnormalities in the gastric antrum is a problem which differs in a number of important respects from that of ulcer of the body and fundus. The incidence of cancer is generally recognized to be higher in the antrum than in the body of the stomach, and a greater proportion of the problematic lesions prove to be malignant. The differentiation between benign and malignant disease of the antrum by means of radiologic examination is often difficult or impossible.

Ulcer craters in the antrum differ from ulcers in the body of the stomach in the following respects: They are frequently associated with other abnormalities in antral contour, including spastic narrowing and irregularities in one or both curvatures of the antrum. If no deformity is present initially, various changes often develop during a course of observation and treatment of an ulcer in that location. A reversion to a normal x-ray picture after an interval of medical therapy usually cannot be anticipated even if the lesion is a benign one.

Some ulcer craters in the antrum unassociated with deformities may heal completely and the antrum may regain an entirely normal appearance. In this event, the diagnostic problem may thereby be resolved like that of ulcer of the vertical portion of the lesser curvature. This applies to only a small proportion of antral lesions.

In general, it is useful to consider all types of deformity of the antrum due to benign processes as a single radiologic entity, so-called benign antral disease or antral gastritis.[79, 80, 81] There are many radiologic features common to this entity and to antral carcinoma.

The chief radiologic features include prepyloric narrowing of varying degree, abnormal, stiff, irregular peristalsis, exaggeration or diminution in the caliber of mucosal folds, delay in emptying and, in some cases, changes due to hypertrophy of the pyloric muscle. Narrowing of the antrum occurring in benign disease is commonly associated with peptic ulcer in the antrum, on the vertical portion of the lesser curvature or in the duodenum. The abnormal appearance of the antrum usually persists after healing of the ulcer has occurred. Approximately three quarters of those patients who present the x-ray picture of antral gastritis either have, or have had at some

previous time, a peptic ulcer in the stomach or duodenum.[82-85] Similar radiologic deformities of the antrum may also occur in individuals without any evidence of associated disease. Identical radiologic abnormalities are also occasionally attributable to other disease processes, such as pancreatic rests or the rarer neoplasms.

Benign antral disease or antral gastritis gives a rather static type of x-ray picture which tends to persist and often is little influenced by a program of ulcer therapy. Serial x-ray examinations often fail to resolve the problem. Narrowing of the antrum and other radiologic abnormalities commonly remain after a period of medical management, and repeated x-ray examinations continue to show evidence of a disease process.

Gastric analysis may at times be of value as an aid in the differential diagnosis between benign and malignant antral disease. If there is radiologic evidence of ulceration, the finding of histamine achlorhydria indicates malignancy. In the absence of ulceration, achlorhydria can be encountered with either a benign or a malignant process.

Gastroscopic examination of patients with radiologic evidence of antral disease yields findings which are of interest. Spasm of the antrum which has been shown on radiologic examination is not found in the majority of instances under the conditions of gastroscopic examination, a difference which aids in differential diagnosis. The difference in the contour of the antrum is probably due to the large volume of air which is instilled into the stomach at the time of gastroscopy. A good view of the distal antrum and of pyloric closure can usually be obtained at gastroscopy. The examination is often of assistance in the differentiation between spasm and organic narrowing in patients with radiologically demonstrated antral constriction. The significance of irregularities in the outline of the antrum seen on x-ray can also be evaluated if the areas in question are visualized at gastroscopy. Information may be obtained concerning the benign or malignant nature of ulceration. Various types of gastritis, if present, may likewise be identified by the gastroscopic method. Superficial, hypertrophic or atrophic gastritis as defined gastroscopically are noted in many patients with benign antral disease. Since the gastroscopic changes of gastritis are also frequently found in other situations, their significance is problematic and they are now generally regarded as quite unrelated to the radiologic picture of "gastritis."

The over-all accuracy of gastroscopy in antral disease is about 85%.[84] The most common source of error is inability to obtain an adequate view of the antrum and pylorus. Under such circumstances a negative examination must usually be regarded as noncontributory. When a satisfactory view of the antrum has been obtained in a patient with antral narrowing by x-ray, the findings may be reassuring. However, a malignant process may occasionally be overlooked. When the process is a benign one, erroneous interpretation of the picture as malignant is infrequent.

A recent study of a series of patients with antral disease yielded data which bear on several important aspects of the problem.[86] The group for study was composed largely of patients in whom the diagnosis had been in doubt on the basis of the clinical and x-ray findings. Thirty per cent of the patients were subsequently found to have carcinoma, verified with few exceptions at operation. The five-year survival rate for this group with carcinoma was 23%. Further study indicated that this rather high salvage rate could be attributed to the fact that a number of the patients had small lesions of a favorable type. It appeared that carcinoma of the antrum, which produces equivocal x-ray findings, quite often may prove to be amenable to surgical treatment. An aggressive surgical approach is therefore justified in patients with antral disease whenever there is continuing reasonable doubt as to the nature of the underlying process. Such a policy may result in the salvage of a gratifying proportion of the patients with gastric cancer who present this type of x-ray problem.

Other Special Diagnostic Problems

Several other clinicoradiologic entities deserve special consideration. Ulcer craters located at or near the greater curvature of the stomach as seen radiologically are more often malignant than benign. In Smith and Jordan's series, 60% of such craters were malignant.[74] Silk et al. found that 10 of 18 craters on the greater curvature were due to malignancy.[87] There is general agreement that early surgical intervention is indicated in patients with greater curvature ulcers because of the high incidence of malignancy in this type of lesion.

Ulcer craters located high in the stomach near the cardia present a special problem in management if diagnostic studies fail to resolve the problem. A diagnostic laparotomy may become necessary. However, an extensive resection which includes the sacrifice of the cardiac sphincter for lesions found to be benign should be avoided if at all possible. Biopsy of the lesion with frozen section may prove to be of great value. Lattes and Harvey have recently reported a method of biopsy of gastric lesions at the time of operation for diagnosis by frozen section technic.[88, 89] These workers open the stomach and visualize the ulcerative lesion through a short proctoscope which has been introduced through the gastrostomy. Multiple biopsies are then taken from the edges and floor of the lesion and studied by means of frozen section. A diagnostic accuracy of 97% has been attained by this method. Of a total group of 132 biopsies, according to these workers, 23 patients were demonstrated to have malignant disease. Four patients with malignancy had negative biopsies. There were no false-positive results. The false-negative biopsies comprised two small ulcerating lymphosarcomas which were mistaken for inflammatory tissue; one other biopsy consisted of necrotic tumor tissue which was not recognized as such; the biopsies in the fourth case were not taken from representative areas.

The patient with x-ray evidence of wide folds in the stomach may also present a problem in differential diagnosis. The radiologic demonstration of wide gastric rugae at times suggests the possibility of infiltration of the gastric wall either by carcinoma or by the rarer gastric neoplasms. Such folds may assume a polypoid appearance. They may be distributed diffusely throughout a large part of the stomach, or may appear as localized collections of wide rugae. This type of radiologic picture also occurs quite commonly in the absence of malignant disease, and the nature of the process is often in doubt. Differential diagnosis by means of x-ray examination is particularly difficult if the process is localized in one portion of the stomach. Gastroscopic examination may resolve this problem. At gastroscopy the stomach wall frequently proves to be normal in appearance after adequate insufflation with air. If the gastroscopic appearance also proves to be suspicious, biopsies may be taken by means of the operating gastroscope.[84] When doubt persists as to the diagnosis, surgical exploration and direct inspection of the interior of the stomach are sometimes necessary to resolve the problem.

A rather large proportion of patients with carcinoma of the fundus constitutes yet another group in whom the diagnosis may be difficult to establish.[90] Negative or indeterminate x-ray findings are encountered in an appreciable number of such individuals, although suggestive symptoms may be present. When the symptoms suggest a high gastric lesion and radiologic studies are negative, esophageal bougienage may be helpful. This procedure may be performed using either a flexible gastroscope or a stomach tube which contains a flexible metal obturator. When a high gastric lesion is present, palpation of the region of the cardia by means of bougienage frequently reveals a point of fixed obstruction.[91, 92, 93] At times the point of fixed obstruction may be demonstrable before dysphagia has developed. If such obstruction is detected or suspected, endoscopic examination by the appropriate technic may be undertaken to obtain a biopsy for definitive diagnosis.

Results of Surgery

Current figures for the five-year cure rate for carcinoma of the stomach reported from the large private clinics fall roughly between 5 and 10% of all patients admitted to the hospital for carcinoma. In Minneapolis a recent five-year survival rate of 12.2% was reported.[94] In New Orleans 9.9% five-year survivals were recorded by Ochsner and Blalock.[95] In Rochester, Minnesota, the five-year cure rate has recently reached 14%.[96]

It is noteworthy that the best results of surgical treatment are those reported from the large private clinics. Obviously, the patients who chance to go to such clinics represent a somewhat selected group, because of economic and numerous other factors. Hence, better results can probably be anticipated from such institutions as compared with large municipal hos-

pitals. It is also noteworthy that results of surgery for carcinoma of the stomach have improved substantially in recent years. In the Presbyterian Hospital in New York City the five-year cure rate has risen from 2.5% to 8% in the last four decades.[51] This improvement in surgical results is probably due both to technical advances and to earlier diagnosis of cancer, although it is difficult to be sure which factor is the more important.

Technical advances are evident from the fact that a higher proportion of patients with cancer of the stomach have been subjected to surgical intervention in recent years than formerly, and the proportion of the patients who undergo resection has likewise increased. At the present time, in many clinics, well over 75% of patients with carcinoma are considered to be suitable for surgical exploration. The proportion of patients who undergo resection has now risen to approximately 50% in the large private clinics. The incidence of total gastrectomy has also risen.

Improvement in surgical technic is also reflected in lower mortality figures in recent years. The risk of the various operative procedures during earlier years is shown in the following representative figures quoted from Ochsner and Blalock. These authors recorded mortality rates for the various operations for carcinoma carried out during the years 1942 to 1951, as follows:[95]

Esophagogastrectomy	50%
Total gastrectomy	30%
Palliative procedures other than gastrectomy	18.2%
Exploratory	13.4%
Curative subtotal resection	9.5%

The above figures are of interest in three respects. The mortality rates for all types of resection were significantly higher at that time than they are today. The figures also illustrate well the relative gravity of the various types of operation. It is also apparent that exploration alone, or simple palliative operations such as may be performed on patients with advanced disease, will be attended by a rather high hospital mortality rate.

Recent mortality figures for subtotal gastrectomy for carcinoma are quite low. At the Massachusetts General Hospital, for example, the recent mortality rate for subtotal gastrectomy for cancer is 4%.[97] In Minneapolis, a rate of 5% was recently reported.[98]

For total gastrectomy the current mortality rate is approximately 20 to 30% in the reported series.[97, 99, 100, 101] Ransom has recently reported a mortality rate of 18% for total gastrectomy in a rather large series of patients. Esophagogastrectomy is likewise attended by a high risk, with an operative mortality roughly comparable to that for total gastrectomy.

These extensive operative procedures—total gastrectomy and esophagogastrectomy—have resulted in five-year cures of gastric carcinoma for lesions which certainly could not have been cured by a less extensive surgical procedure. Ransom reported five survivors among 48 patients who underwent this procedure for extensive carcinoma. Others report encouraging results,

but the number of patients in the various reports is small. Occasional five-year cures are also reported for the procedure of esophagogastrectomy for adenocarcinoma.

A number of factors play an important role in prognosis after definitive surgery for gastric cancer. The duration of symptoms, the location and extent of the tumor and its morphologic characteristics are all factors of major importance. The formulation of the prognosis in carcinoma of the stomach depends chiefly upon data which can be ascertained with certainty only by operative intervention.

The duration of the disease before operation is obviously a factor of major importance in prognosis. However, the effect of the time factor is variable. Some patients with a lesion known to have been present for many months and in whom operation has been delayed may still be found to have a resectable tumor. Examples are on record of patients with lesions that had been present for several years which have been found to be resectable after a long delay.

The long history of gastric symptoms preceding the establishment of the diagnosis of carcinoma in many patients has been emphasized repeatedly. The importance of avoiding delay in the recognition of the disease cannot be overemphasized. Nevertheless, the extent to which delay in diagnosis affects prognosis is not established, and it seems that other factors which are concerned with the biologic characteristics of the tumor are probably more important in determining the outcome.

The most important factor in prognosis is the presence or absence of lymph node metastases at the time of operation. When no metastases are found, subtotal resection results in a five-year survival rate which ranges between 40 and 50%.[102]

The prognosis varies with the gross morphologic characteristics of the tumor as found on pathologic study of the operative specimen. While several different pathologic classifications of gastric cancer have been proposed, it appears that the essential differences in prognosis depend on whether the growth of the tumor is primarily in the mucosal layer of the stomach, inward with predominant intrusion into the lumen, outward with penetration through the gastric wall, or diffusely through the various coats of the organ.[51] According to the classification of Stout, the following were the percentages of survivors as related to morphologic types: superficial spreading, 54%; fungating, 36%; penetrating, 12%; and linitis plastica, none, in the records of the Presbyterian Hospital in New York prior to 1946.

Prognosis is affected by the location of the lesion. Patients with growths located high in the fundus or at the cardia usually have a poor outlook. Patients with growths situated in the pars media apparently have a slightly better than average outlook.[51]

The size of the lesion is of definite prognostic significance in patients with gastric cancer. When the growth is small the outlook is more

favorable.[103] Moreover, the patient with a small lesion has been shown to have a more favorable prognosis if there is an ulcer type of history, or if there is high gastric secretory activity or a roentgenologic picture consistent with that of benign ulcer.

It is unfortunate that not much can be stated concerning prognosis in individual cases on the basis of clinical data before operation. As stated earlier, most of the factors in prognosis are difficult or impossible to ascertain ante-operatively. This applies in particular to the presence of lymph node metastases and to a large degree to the morphologic classification of the lesion. The type and extent of the lesion are difficult to appraise by means of clinical study. Radiologic examination and gastroscopy may at times supply a limited amount of information, particularly if the tumor is of the fungating type.[104]

There is some evidence which suggests that patients with carcinoma in whom the diagnosis is uncertain on the basis of radiologic findings have a better than average outlook. Harvey and Hennig [105] have recently found a higher five-year cure rate among those patients who have indeterminate radiologic findings than among those in whom the diagnosis is relatively obvious. As noted earlier, carcinoma of the antrum in which the radiologic picture resembles benign disease has been found to give better surgical results.

Disorders Which Result from Gastrectomy

The increased frequency with which total gastrectomy is being performed has given rise to numerous problems in postoperative management. Study of these problems has contributed materially to the understanding of gastric physiology. Many of the same disorders can also occur in patients who have undergone only a subtotal gastrectomy. However, after the latter procedure these disorders are less marked and are often overshadowed by the effects of the underlying disease process.

The removal of part or all of the stomach can cause a number of important nutritional disorders. These are attributable in part to the loss of the reservoir function of the stomach and the consequent reduction in the quantity of food which is ingested. There is, in addition, an impairment in the absorption or utilization of various nutrients. Gastric resection may also give rise to a variety of symptoms which are usually grouped together under the heading of the dumping syndrome. These various untoward results of operation are problems which may require continuing medical management.

The physiologic mechanisms which are disturbed by gastric resection are most clearly manifested in patients with total gastrectomy. The following comments apply chiefly to this group. It appears, however, that similar disorders, when they occur after partial resection, are usually on a similar physiologic basis.

Rapid Intestinal Transit

Radiologic study of patients with total gastrectomy shows that barium enters the upper loops of the small bowel with a rush. Thereafter, during the x-ray examination, the rate of movement of the barium column is variable and, at times, the progress may be very slow.

It has been suggested that intestinal hurry may be the basis for the diarrhea which may occur after gastrectomy. However, the importance of rapid transit alone as a cause of diarrhea is difficult to assess. A variety of other factors, such as unabsorbed fat in the intestinal contents, may also be important. Diarrhea is a frequent complaint in the early weeks after total gastrectomy. In many patients it tends to subside gradually.

Subtotal gastrectomy likewise may result in diarrhea. Rapid transit through the small bowel might also play a rôle here. Anticholinergic drugs at times appear to be effective in controlling the diarrhea, an observation which supports the view that rapid transit may be an important factor in the production of this symptom.

Impaired Fat Absorption

Total gastrectomy with direct esophagojejunal anastomosis and bypassing of the duodenum results in steatorrhea.[106, 107, 108, 109, 110] Thirty per cent or more of the ingested fat is found in the feces when the patient is on an average mixed diet. The mechanism responsible for this steatorrhea is not fully understood. However, there is some evidence to support the view that the impaired utilization of fat is due, at least in part, to incomplete mixing of food with bile and pancreatic juice and resulting incomplete digestion. Operations which allow the duodenum to be bypassed not only result in inadequate mixing of food with digestive enzymes, but it is also hypothesized that rapid transit of food through the jejunum may reduce the amount of time available during which digestion can occur. As mentioned above, the importance of intestinal hurry is not fully understood.

The establishment of esophagoduodenal continuity, such as by the use of jejunal transplants interposed between esophagus and duodenum in patients with total gastrectomy, has been shown to result in better fat absorption. This surgical procedure presumably permits better mixing of food with bile and pancreatic juice, and greater amounts of fat are digested and absorbed as a result.[110]

It is also quite possible that the nervous and hormonal stimulation of pancreatic secretion is impaired by total gastrectomy, and that this may result in steatorrhea. The operative procedure sacrifices the vagus nerve and also probably impairs hormonal stimulation of the pancreas by bypassing the duodenum. Although patients with total gastrectomy have been shown to retain the ability to secrete pancreatic juice normally in response to secretin, the mechanisms which can provide such stimulation may be interfered with.[111]

Possibly the difference in pancreatic stimulation is partial rather than absolute. Increase in the fat content of the diet in patients with total gastrectomy results in an absolute increase in fat absorption. There is also some evidence that small, frequent feedings result in a better absorption of fat than occurs on three meals a day in patients with total gastrectomy. This may be explained by the assumption that the ingestion of food every few hours serves as a more continuous and a more effective means of stimulating pancreatic secretion than if only three meals are ingested in the course of 24 hours.

The dietary management of patients with total gastrectomy is usually most effective if a high fat intake is prescribed with six to eight feedings per day. The use of pancreatin and oxbile extract is reported to decrease the output of fecal fat. Other emulsifying agents have also been found to be of value.[112]

Some increase in the output of stool fat has also been found in patients who have undergone subtotal gastrectomy. The amount of unabsorbed fat is usually small.[113] In some patients the amount of steatorrhea is clinically significant. In most nutritional problems encountered after subtotal gastrectomy, the impaired utilization of fat is probably of little importance.

Impaired Nitrogen and Carbohydrate Absorption

It seems unlikely that impaired utilization of nitrogen is often of much importance in patients who have had either a total or a subtotal gastrectomy. An increase in the output of fecal nitrogen does occur in some patients after total gastrectomy. The 24-hour output may be found to be somewhat in excess of the normal figure of 2 gm. but not large enough to be of major practical importance. Protein utilization has also been assayed by means of a gelatin tolerance test and normal results have been reported.[114]

The ability to digest and absorb carbohydrates is also not markedly disturbed after total gastrectomy. The abnormality in carbohydrate absorption which does result after surgical procedures on the stomach is related to the dumping syndrome.

Impaired Utilization of Vitamins

Absorption of vitamin B_{12} is interrupted in patients with total gastrectomy. When vitamin B_{12} which has been labeled with radioactive cobalt is administered orally to patients with total gastrectomy, 80 to 100% of the administered material appears in the feces.[115] The oral administration of radioactive vitamin B_{12} after total gastrectomy also fails to result in a demonstrable hepatic uptake of radioactive material such as occurs in the normal individual.[116] Evidence of failure of absorption of vitamin B_{12} after total gastrectomy has also been obtained by the use of the Schilling test. Orally administered vitamin B_{12} fails to appear in the urine in patients

with total gastrectomy after a flushing injection of the vitamin.[117, 118] The failure of absorption of vitamin B_{12} is attributed to the loss of intrinsic factor which results from total gastrectomy. It is now apparent that in the human being the stomach is the only source of intrinsic factor. Total removal of the stomach therefore results in the appearance of a macrocytic anemia.

The macrocytic anemia does not develop until two or three years after operation. This delay is attributed to the storage of vitamin B_{12} in the liver before operation. It appears that sufficient vitamin B_{12} is present in the normal liver to supply the needs of the organism for at least two years. The primary anemia which appears after total gastrectomy can be controlled or prevented by the administration of vitamin B_{12} parenterally. The daily requirement is estimated to be 1 μg.

Primary anemia is rarely observed in individuals who have undergone subtotal gastrectomy. Even those patients who have been subjected to a nearly total gastrectomy fail to develop primary anemia. On the basis of such clinical observations it is apparent that a very small portion of the cardiac end of the stomach will supply an adequate amount of intrinsic factor.

The effect of gastric resection upon the utilization of the other members of the B complex is less well understood. It has been suggested that folic acid deficiency does develop occasionally in patients with total gastrectomy. The evidence for folic acid deficiency is chiefly the fact that a primary anemia sometimes occurs which fails to respond completely to treatment with parenteral vitamin B_{12} but is corrected when the treatment is supplemented with folic acid.[119, 120, 121]

Occasional patients develop signs that suggest riboflavin deficiency following either total or subtotal gastrectomy. Glossitis, cheilosis, angular stomatitis and dysphagia may be observed. These changes may be relieved by treatment with parenteral vitamin B complex.[109, 122]

Deficient utilization of the fat-soluble vitamins may also occur after total or subtotal gastrectomy. Low serum carotene and vitamin A levels may be encountered. Occasionally the prothrombin time is found to be somewhat prolonged, indicating some impairment of vitamin K absorption.

Impaired Utilization of Minerals

The utilization of food iron may be impaired as a result of either total or subtotal gastrectomy. Serum iron levels tend to be low in some patients after operation. If iron is administered orally the serum values rise in some patients but not in others.[123, 124]

Theoretically, defective utilization of iron may be attributable to the loss of hydrochloric acid and consequent impairment in the conversion of food iron into the absorbable ferrous form. Exclusion of the absorbing surface of the duodenum by a bypassing procedure may also be an important factor in impairment of the absorption of iron.[125] The duodenum constitutes the

area in the gut where the iron absorption is maximal under normal conditions. It is bypassed by the gastric contents as they enter the intestine after most gastric resections.

The amount of iron present in storage before operation may be important in relation to the possible development of anemia after gastrectomy. In the normal individual, iron stores are sufficient to prevent anemia for a long time if there is a deficient intake or absorption of iron. However, many patients who are subjected to operation for gastric disease have suffered a depletion in iron stores as a result of blood loss or other factors before operation. At the present time, the importance of these various factors in the pathogenesis of anemia after gastrectomy is incompletely understood.

Hypochromic anemia is common after partial or total gastrectomy. It may respond to the oral administration of iron in conventional dosage. In some patients the oral administration of iron is ineffective, and parenteral injection is necessary.

Total gastrectomy also apparently has an adverse effect upon calcium balance. Available data concerning this problem are scanty, but it appears that an impairment in the absorption of calcium occurs in some individuals. This may be due to the formation of insoluble calcium soaps in the intestine. Vitamin D deficiency may play a rôle here.[126, 127]

Dumping Syndrome

Most of the other adverse effects of total or subtotal gastrectomy have been grouped together under the heading of the dumping syndrome. The most common of these problems is the so-called early syndrome. Patients with this difficulty complain of abdominal fulness, weakness, sweating, palpitation and sometimes vomiting. The symptoms appear during or shortly after the ingestion of food and may last for from 20 minutes to an hour. Relief of symptoms usually occurs upon the patient's assuming the horizontal position.

Numerous hypotheses have been proposed to account for early dumping symptoms.[128] At the present time the problem remains a controversial one. It appears that changes in plasma volume may be of importance. The passage of food into the jejunum causes a shift of fluid from the bloodstream to the bowel lumen as a result of differences in osmotic pressure. A fall in plasma volume of considerable magnitude may ensue and be associated with vasomotor symptoms.[129] Rapid distention of the jejunum may be responsible for some of the symptoms, such as abdominal fulness, nausea and vomiting. Whatever may eventually prove to be the mechanism of early dumping symptoms, it seems quite clear that the symptoms are more common in patients with high resections than in patients with low resections.

The majority of patients who have undergone total gastrectomy suffer from the early dumping syndrome. The various therapeutic measures available for the management of this problem may be helpful but yield

uneven results. The assumption of the horizontal position after meals is the most effective measure for control of the symptoms. Avoidance of all fluids at mealtime is often helpful. A diet rich in protein and low in carbohydrate may be better supported and is thought to result in a less rapid shift of fluid from bloodstream to jejunum. Anticholinergic drugs also are helpful for the relief of symptoms. Any of these measures may be useful in the treatment of patients with the dumping syndrome after either total or subtotal gastrectomy.

Symptoms which appear at a later time interval after the ingestion of food may be attributed to a different mechanism.[130] After gastrectomy the oral glucose tolerance test is characterized by a rapid rise in blood sugar to high levels within a short period of time, followed by a drop to a subnormal level after about two hours. The secondary fall in blood sugar is thought perhaps to be due to a temporary inhibition of glycolysis produced during the period of hyperglycemia.

Patients with total or subtotal gastrectomy may exhibit hypoglycemic symptoms approximately two hours after a meal. Weakness, palpitation and sweating may develop. Such symptoms are associated with a low blood sugar and are promptly relieved by the ingestion of carbohydrates.

One additional complication which arises after total gastrectomy is that of regurgitant esophagitis. Operations that sacrifice the cardiac sphincteric mechanism may result in the appearance of this syndrome. Radiologic study of such patients may demonstrate that barium flows back readily into the esophagus. It appears that after a total gastrectomy has been performed the small bowel contents may regurgitate freely into the esophagus in a similar manner. Esophagoscopic examination sometimes reveals inflammatory changes in the mucosa of the distal esophagus. Heartburn, regurgitation and substernal pain are the typical symptoms. The treatment of regurgitant esophagitis gives rather unsatisfactory results. The avoidance of the recumbent position should be advised, particularly after meals.

In summary, the currently recommended program for the medical management of patients who have undergone total gastrectomy embodies the following principles: the diet should be high in fat and protein content; carbohydrates should be proportionately small in amount; small, frequent feedings up to the number of eight per day may be desirable, and fluids should be largely avoided at mealtimes; a mixture of supplementary vitamins should be given.

Hypochromic anemia can usually be treated successfully with oral iron. A liquid preparation is preferable. Parenteral vitamin B_{12} will eventually be required by the patient with total gastrectomy. Pancreatin, oxbile extract or other emulsifying agents may be useful for the correction of deficient digestion and absorption of fats.

The symptoms classified under the heading of early dumping syndrome are also helped by a low carbohydrate, dry diet, and by the patient's lying down after meals, if possible. Anticholinergic drugs may be valuable.

For patients who have been subjected to subtotal resection, similar dietary measures and medications may be employed when the clinical picture warrants it. However, the dumping syndrome is rather uncommon after subtotal resection for cancer, and the nutritional problems are much more apt to be due to the carcinoma.

Inoperable and Recurrent Carcinoma

Most patients who present clinical evidence of gastric carcinoma require a laparotomy to establish a definitive diagnosis and to determine operability. In a small proportion of patients, operation can be avoided if a biopsy of a cervical lymph node or other metastatic site establishes the diagnosis. Another small percentage of patients may be regarded as inoperable because of poor general condition or other associated organic disease. Hepatomegaly alone does not necessarily constitute a contraindication to surgery. Hepatic enlargement may be due to coincident disease and, moreover, tissue diagnosis is usually desirable to rule out the possibility that a rare radiosensitive tumor is present.

The average survival time for all patients with carcinoma of the stomach after operation is less than two years. When the resection has been a palliative measure, the average time of survival is less than one year. When laparotomy without resection has been performed, the average time of survival is approximately four months.[98, 131]

Radiotherapy is generally regarded as of little or no value in the treatment of carcinoma of the stomach. Most cancers of the stomach are highly resistant to irradiation. Moreover, the side-effects of radiation may be extremely distressing to an already debilitated patient. Direct irradiation of inoperable cancer of the stomach in the operating room during laparotomy has been attempted and some improvement recorded in a few patients.[132]

In rare patients whose general condition is good, external irradiation has been used with some apparent benefit. Symptomatic improvement and shrinkage in tumor size as determined by radiologic examination have been recorded. This type of treatment has been used in patients who are in good general condition and who decline surgery. Radiotherapy should rarely be employed in patients who exhibit evidence of recurrent disease after operation, except as a measure of relief of pain.

The question of a second operation arises at times in patients who present evidence of recurrent disease which may be limited to the gastrointestinal tract. While a second procedure may be needed for palliation, it is doubtful whether such a procedure ever results in cure in patients with recurrent symptoms due to cancer. Recently Wangensteen carried out a series of second operations in patients clinically free from evidence of recurrence six months after operation, in an attempt to salvage some patients who have early recurrences.[94] The results of this approach will be of interest from both a practical and a theoretic standpoint.

As a rule, the program of management of patients with recurrent or inoperable carcinoma of the stomach is limited to supportive therapy. Treatment is largely limited to the use of appropriate sedatives and the judicious employment of other measures for symptomatic relief. One of the main roles of the physician is that of providing moral support for the patient with a completely unfavorable outlook.

Future Trends

Recent advances in surgical technics for treatment have been reflected in a modest increase in the percentage of patients cured of gastric carcinoma. This change is attributable to such factors as a diminished operative mortality, a higher resection rate and the perfection of technics for more radical operations. It seems probable, however, that the surgical approach to the disease is approaching its maximal possibility of effectiveness, and that further improvement in the results of therapy will be due to other factors.

Delay in operation remains an important problem, which contributes to the poor over-all results in this disease. Earlier diagnostic studies of patients with significant symptoms and earlier surgery when cancer is suspected should result in continued improvement in results. Those groups of patients with x-ray findings of indeterminate significance merit special study in an effort to increase the proportion of individuals who may be discovered to have a small, curable lesion.

Current investigations which relate to the etiology of the disease, such as its relation to geographic and soil factors, may result in new approaches to the more fundamental aspects of the problem. It may also be hoped that studies of those gastric disorders which seem to be premalignant will provide new clues as to etiology and also result in a more practical approach to the detection of cancer during its preclinical, asymptomatic phase.

Summario in Interlingua

Ben que pauco es cognoscite relative al etiologia de carcinoma gastric, plure factores de definite signification pote esser identificate. Factores hereditari es manifeste in le occurrentia familial del morbo e in le facto que un plus forte tendentia al disveloppamento de carcinoma gastric es a notar inter individuos del gruppo de sanguine A. Influentias del milieu es indicate per le extense differentias in le incidentia del morbo in varie paises e in varie areas del mesme pais.

Le hypothese ha essite formulate que un previe vulneration del stomacho es essential in le disveloppamento de carcinoma gastric. Il es ver, per exemplo, que achlorhydria es un precursor commun de morbo maligne. Gastritis atrophic e anemia perniciose predispone possibilemente al disveloppamento de cancere. Polypos adenomatose es usualmente considerate como portatores de potentialitate maligne, sed iste conception es questionabile. Certe autores crede que patientes con ulcere peptic curre un plus alte risco de disveloppar cancere.

Studios in grosso visante a deteger cancere silente ha revelate le presentia de morbo maligne del stomacho in circa un patiente per mille per anno in gruppos de etate plus avantiate. A causa de iste basse rendimento, programmas de detection de

cancere gastric ha essite concentrate super individuos con disordines premaligne del stomacho, i.e. per exemplo achlorhydria e anemia perniciose.

Durante le phase symptomatic, carcinoma del stomacho es facile a recognoscer super le base del constatationes clinic e radiologic, sin ulle studio additional, in circa 80% del patientes. In le altere 20% del casos, le constatationes radiologic es indeterminate o—in un micre procentage—negative.

Gastroscopia es utile in le studio de patientes in qui le exacte natura del constatationes roentgenographic non es clar. Le diagnose cytologic ha etiam attingite satis alte grados de fidelitate inter le manos de expertos e representa un adjuta de valor in le examine de patientes con lesiones gastric.

Le possibilitate de carcinoma debe esser prendite in consideration in le majoritate del patientes con benigne lesiones del stomacho. Ulceres al portion vertical del curvatura minor es evalutate le melio per studios radiologic in serie, effectuate durante un rigide programma de therapia medical pro ulcere benigne. Le examine gastroscopic e le studio cytologic revela a vices signos de malignitate e resulta assi in un expedition del therapia chirurgic. Studios a uropepsina se ha provate de limitate valor diagnostic.

Morbo antral de natura benigne sed resimilante carcinoma antral require frequentemente un studio per medio de omne le disponibile methodos diagnostic. Il non es rar que studios roentgenologic in serie non succede a resolver iste typo de problema. In casos in que le diagnose remane dubitose, intervention chirurgic es frequentemente indicate.

Le introduction recente de biopsia con sectiones congelate al tempore del operation se ha provate de valor in tanto que illo pote evitar un chirurgia innecessarimente radical in patientes in qui le lesiones gastric es subsequentemente recognoscite como de character benigne.

Al tempore presente le proportion de curationes quinquenne post carcinoma del stomacho tractate in le major clinicas private es circa 5 a 10% de omne le patientes.

In patientes sin metastases a nodos lymphatic le superviventia quinquenne amonta a inter 40 e 50%. Le prospectos es relativemente favorabile in patientes qui exhibi un aspecto radiologic que es compatibile con le presentia de un lesion o benigne o maligne, como per exemplo benigne morbo antral.

Patientes qui ha essite subjicite a gastrectomia total require usualmente un regime postoperatori. Isto resulta generalmente in un aspecto de malnutrition con steatorrhea, deficientias de varie vitaminas, e le syndrome de discarga. Le tractamento de patientes con recurrentia de carcinoma o carcinoma de character inoperabile remane in essentia un tractamento supportative.

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THE USE OF RADIOACTIVE PHOSPHORUS IN THE THERAPY OF LEUKEMIA, POLYCYTHEMIA VERA AND LYMPHOMAS: A REPORT OF 10 YEARS' EXPERIENCE*

By Robert B. Chodos, M.D., F.A.C.P., *Syracuse, N. Y.*, and Joseph F. Ross, M.D., F.A.C.P., *Los Angeles, California*

Radioactive phosphorus is now generally accepted as an effective therapeutic agent for chronic leukemia and polycythemia vera. There is some disagreement, however, as to how it should be used in the treatment of patients with chronic leukemia. In most clinics, therapy of chronic leukemia with radiophosphorus has been initiated by the "fractional" or "saturation" methods of Low-Beer et al.[16] Subsequent dosage has depended upon the clinical and hematologic response of the individual patient,[2, 7, 10, 11] with additional radiophosphorus being administered only when there was evidence of progression of the disease. The resulting length of survival has been approximately that obtained with x-ray therapy.[2, 7, 8, 11, 12]

More recently, Osgood and his associates have challenged this concept. They have presented data suggesting that continuous titrated therapy, either with radiophosphorus or x-ray, may be more effective in prolonging life in chronic leukemia and in making the life of the individual patient more comfortable and useful.[13–15, 30]

It is the purpose of this report to summarize our 10 years of experience with radioactive phosphorus in the clinical management of patients with leukemia, lymphoma and polycythemia vera. Therapy was individualized, and radioactive phosphorus was given only when there was evidence of progression of the disease. No effort was made to restrict treatment to radiophosphorus.

The results observed are discussed in relation to reports in the literature which summarize other experience in the treatment of these diseases. Our method of treatment in each disease is outlined, and the immediate and long-term response to this therapy is described.

I. Clinical Material and Methods

The 71 patients included in this survey were studied and treated at the Massachusetts Memorial Hospitals from April, 1944, when the initial course

* Received for publication January 28, 1957.

From the Robert Dawson Evans Memorial and Massachusetts Memorial Hospitals, and the Department of Medicine, Boston University School of Medicine, Boston.

A portion of this work was supported by a grant from the Atomic Energy Commission to the Massachusetts Memorial Hospitals.

Requests for reprints should be addressed to Robert B. Chodos, M.D., Veterans Administration Hospital, Syracuse 10, N. Y.

of radioactive phosphorus was administered, to April, 1954. Treatment of the last patient included in this series was initiated on July 31, 1952.

The established diagnoses were: chronic granulocytic leukemia, 30; chronic lymphocytic leukemia, 12; polycythemia vera, seven; multiple myeloma, seven; Hodgkin's disease, four; acute leukemia, eight; chronic monocytic leukemia, one; mycosis fungoides, two.

The diagnosis of leukemia and myeloma was based upon a study of the peripheral blood, sternal marrow and the clinical manifestations of the patients. The diagnosis of Hodgkin's disease was made by lymph gland biopsy. Lymph gland and skin biopsies were both utilized to establish the diagnosis of mycosis fungoides. The criteria for diagnosis of polycythemia vera were a significant elevation of the red cell count, hemoglobin and hematocrit, and usually coexisting elevation of the white blood cell and platelet counts. Cardiac and pulmonary disease that might result in secondary polycythemia was excluded by appropriate clinical and laboratory studies, including, in several patients, arterial oxygen saturation determinations. Clinical observations and hematologic studies were completed before therapy was initiated and were repeated at approximately one-month intervals.

The radioactive phosphorus * was administered intravenously as an aqueous solution of sodium phosphate. The quantity of radiophosphorus given varied, and was dependent upon the disease being treated, its severity and the response of the individual patient. Details of therapy are included in the summary of results and under "Discussion." Supportive and other forms of therapy were used when indicated.

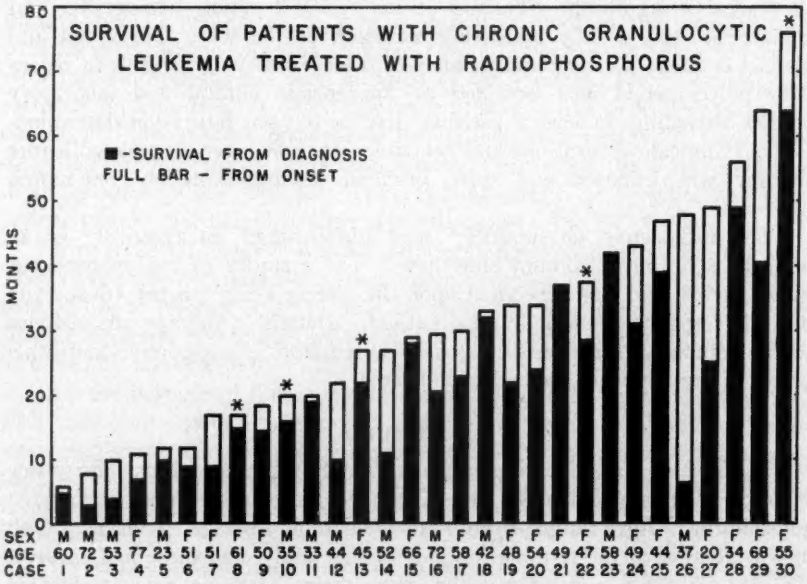
II. Results

A. *Chronic Granulocytic Leukemia:* Thirty patients with chronic granulocytic leukemia (18 females and 12 males) were treated with radioactive phosphorus. Ages ranged from 20 to 77, with an average age of 50. Only five were alive at the termination date of this study, and these had survived 15, 16, 22, 28.5 and 64 months since their diagnosis was established. Twenty-five patients who died survived a mean period of 23 months after diagnosis, with a range of from three to 64 months. Mean survival for the entire group from the presumed date of "onset of the disease" was 30.5 months, with a range of from six to 76 months (figure 1). The median survival since diagnosis was 20 months, and since the onset of symptoms,

* The radioactive phosphorus used for therapy was prepared initially by deuteron bombardment of iron phosphide or red phosphorus in the cyclotron at Massachusetts Institute of Technology, and later by neutron bombardment of sulfur in the uranium reactor at Oak Ridge. The radiophosphorus was standardized by comparison first with a Radium D and E Standard, and later with a Tracerlab simulated P^{32} standard. After 1949 the Tracerlab standards were compared with radioactive phosphorus standards provided by the National Bureau of Standards. Standardization of radioactivity in the solutions used was critical, since discrepancies have been demonstrated between the "millicurie" of solutions utilized in different clinics.[2] Accurately calibrated radiophosphorus in sterile, pyrogen-free solution is now available from several commercial laboratories.

27.6 months (table 5). Seven patients had been treated with x-ray before receiving P^{32}, while 19 received x-ray therapy subsequent to the administration of P^{32}. Transfusions and antibiotics were administered when indicated.

The initial course of radiophosphorus varied from single intravenous injections of 3 to 14 mc. to a total of 20 mc., administered in 0.85 to 9.8 mc. doses at four- to 10-day intervals during a period of up to seven weeks. In response to this therapy, 27 of the 30 patients demonstrated a marked decrease in white blood cell count. The maximal decrease occurred three to 16 weeks after therapy and, on an average, seven weeks after treatment. These and other responses to radiophosphorus are summarized in table 1.


SURVIVAL OF PATIENTS WITH CHRONIC GRANULOCYTIC LEUKEMIA TREATED WITH RADIOPHOSPHORUS
■-SURVIVAL FROM DIAGNOSIS
FULL BAR - FROM ONSET
MONTHS
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CASE 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

FIG. 1. Survival of patients with chronic granulocytic leukemia. All patients except cases 1, 3, 4, 8, 22, 26, 27 and 30 received x-ray during the course of their illness. No specific therapy other than P^{32} was given to cases 1, 3, 8, 22, 26 and 30. The patients indicated by an asterisk (*) were alive as of September, 1953.

The subsequent course of these patients varied considerably. In general, the leukemic process was fairly well controlled with additional P^{32} for periods ranging from three and one-half months to three and one-half years. The white blood count either remained constant—although sometimes at moderately elevated levels—or decreased after additional P^{32}. Hemoglobin was maintained at normal or mildly anemic levels. In many instances splenomegaly recurred and progressed slowly in spite of additional P^{32}. In a few patients splenomegaly did not progress for periods ranging from five months to two years. Hepatomegaly did not recur or progress as

soon after initial P^{32} therapy as did splenomegaly. Weight was maintained and the patients were more comfortable. The course of a patient with chronic granulocytic leukemia treated by P^{32} is illustrated in figure 2.

X-ray therapy to the spleen or spray radiation was administered when P^{32} failed to control the disease. These treatments frequently produced a decrease in white blood count and splenomegaly. However, these responses were of brief duration and the deterioration of the patient was not significantly altered.

A terminal leukopenia was observed in only two of 25 patients. A rise in the white blood count, with many blast cells, occurred in seven patients. Thrombocytopenia was observed terminally in 12 of the 25 patients, but only

TABLE 1

Initial Clinical and Hematologic Response of Patients with Chronic Granulocytic Leukemia to Radiophosphorus Therapy

Clinical	Response	No. of Patients Responding
Splenomegaly	Decreased	22/30†
Hepatomegaly	Decreased	15/24‡
Lymphadenopathy*	Decreased	—
Well being	Improved	24/30
Weight	Increased	18/30
Radiation sickness	None	—
Hemorrhagic manifestations	None	—
Hematologic		
Leukocytes	Decreased	27/30§
Hemoglobin	Transfusion given	13/30
	Increased	9/30
	Decreased	1/30
	No change	7/30
Platelets	Increased	5/30
	Decreased	14/30‖
	No change	8/30

* Not prominent, disappeared when present.
† Maximal response, 3 to 14 weeks; average, 8.5.
‡ Maximal response, 2 to 12 weeks; average, 7.0.
§ Maximal response, 3 to 16 weeks; average, 7.0.
‖ Thrombocytopenia, present in 9, became more marked in 2 to 10 weeks.

six had received P^{32} without supplemental x-ray, nitrogen mustard, aminopterin, steroid or urethane therapy. Hemorrhagic manifestations were observed clinically or at postmortem examination in 10 of the 25 patients. Intracranial hemorrhage was the cause of death in four patients.

In summary, radiophosphorus appeared to be of significant benefit in the management of 27 of 30 patients with chronic granulocytic leukemia and of transient benefit in the remaining three cases. Leukopenia, thrombocytopenia and terminal blastic leukemia were observed after radiophosphorus therapy.

B. *Chronic Lymphocytic Leukemia:* Twelve patients with chronic lymphocytic leukemia received radioactive phosphorus. These patients ranged in age from 41 to 78, with a mean age of 62.4 years. Four were females

and eight were males. Eleven had died by the termination date of this report. The survival since diagnosis of these 11 ranged from two to 86 months, with a mean survival of 28 months (figure 3). The mean survival of the entire group was 34.3 months since diagnosis, and 51 months since the presumed onset of the disease (table 5). If two patients, who were first treated in the terminal phase of their illness are excluded, the mean survival

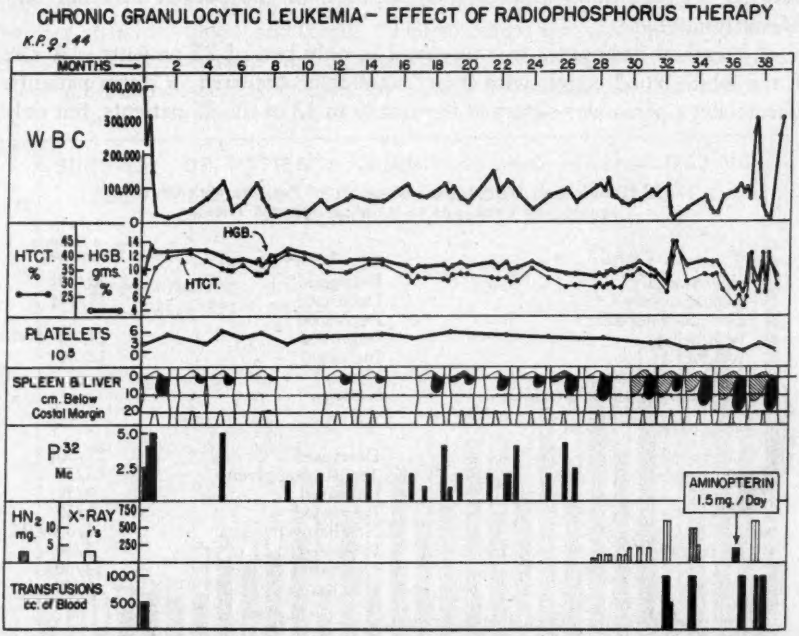
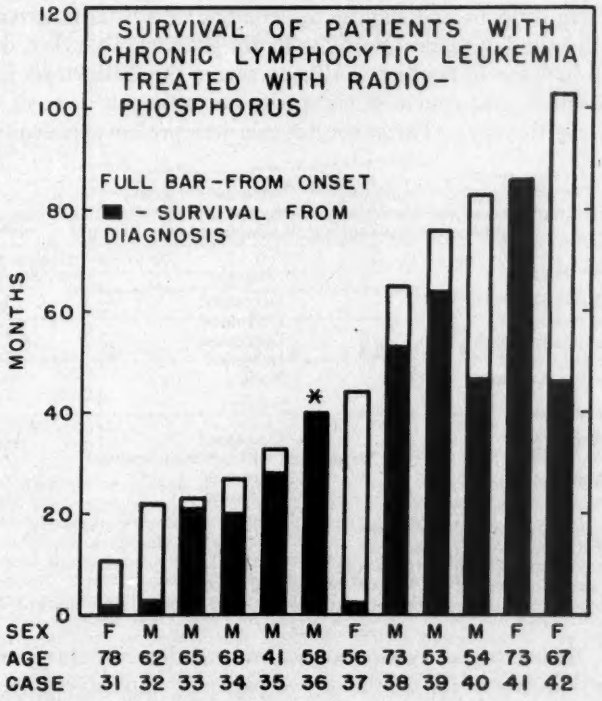


FIG. 2. Radioactive phosphorus therapy of chronic granulocytic leukemia. Case 25, a 44 year old white woman with chronic granulocytic leukemia, was treated with repeated injections of radioactive phosphorus. After an initial course of 19 mc. of P^{32} over a two-week period, the leukocyte count decreased to the normal range. The hemoglobin and hematocrit remained stable after being raised to normal levels by transfusion therapy. Splenomegaly decreased remarkably, and the patient was subjectively much improved. With repeated injections of 1 to 5 mc. of P^{32} at two to 10-week intervals the patient's disease process was controlled for over two years. No transfusion therapy was required during this period. Progressive splenomegaly then occurred. This responded only transiently to x-ray therapy. Anemia also developed, and transfusion therapy was necessary. The patient subsequently failed to respond to nitrogen mustard, aminopterin or x-ray therapy, and died 39 months after diagnosis with an acute blastic leukemia and thrombocytopenia.

time since diagnosis of the remaining nine patients who died is increased from 34 to 41 months. The median survival since diagnosis was 30 months, and since the onset of symptoms, 45 months.

The initial course of radiophosphorus given to this group ranged from 3 to 13.4 mc. In general, individual doses of 1 to 2 mc. were used, although 5 to 6 mc. were administered occasionally. This initial course was

usually administered over a period of from one to 15 days. Therapy covered a period of four weeks in one patient, two months in another, and six months in a third. Two of these three patients who received prolonged fractionated therapy (figure 3, cases 39 and 41) survived 64 and 86 months after diagnosis, respectively. The third patient (figure 3, case 40) received no further P^{32} and died 46.5 months after diagnosis from tuberculosis of the urinary tract rather than as a result of his leukemia. Far less P^{32} was re-


SURVIVAL OF PATIENTS WITH CHRONIC LYMPHOCYTIC LEUKEMIA TREATED WITH RADIO-PHOSPHORUS
FULL BAR-FROM ONSET
■ - SURVIVAL FROM DIAGNOSIS
MONTHS
120
100
80
60
40
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SEX F M M M M M F M M M F F
AGE 78 62 65 68 41 58 56 73 53 54 73 67
CASE 31 32 33 34 35 36 37 38 39 40 41 42

FIG. 3. Survival of patients with chronic lymphocytic leukemia. Case 40 received x-ray prior to the initiation of P^{32} therapy. Cases 35, 36, 38, 41 and 42 were treated with x-ray after P^{32}. No specific therapy other than P^{32} was given to cases 33 and 39. The patient indicated by an asterisk (*) was alive as of October, 1953.

quired for subsequent maintenance therapy in chronic lymphocytic leukemia than in chronic granulocytic leukemia.

Ten of the 12 patients responded to the initial course of P^{32}. The white blood count decreased in all 12 patients. Eleven showed a maximal response in from three and one-half to 10 weeks. One patient who received fractional therapy over a six month period did not respond maximally until 10.5 months after the initial dose. Leukopenia developed in two patients. One of these patients died within two months, while the white blood count

of the other rose to a normal level following x-ray therapy to the spleen. A terminal leukopenia occurred in one patient after extensive x-ray therapy. These and other responses to radiophosphorus therapy are summarized in table 2.

Certain features of the course of these patients may be emphasized. In general, the level of hemoglobin concentration reflected the extent of control of the disease. Transfusions were not required for from nine months to several years in seven of the 12 patients. The platelet count, initially normal in five patients, and slightly to definitely depressed in seven patients, showed a definite but modest decrease in six patients, a marked decrease in one and an increase in another. Mild to severe thrombocytopenia occurred during the subsequent course of eight patients, although three of these also received x-ray therapy. Thrombocytopenia was present terminally in seven

TABLE 2

Initial Clinical and Hematologic Response of Patients with Chronic Lymphocytic Leukemia to Radiophosphorus Therapy

Clinical	Response	No. of Patients Responding
Splenomegaly	Decreased	3/6*
Hepatomegaly	Decreased	5/10†
Lymphadenopathy	Decreased	8/11
Weight	Increased	5/12
Radiation sickness	None	—
Hematologic		
Leukocytes	Decreased	12/12‡
Hemoglobin	Maintained without transfusion	7/12§
Platelets	Decreased	7/12‖
	Increased	1/12

* Maximal response in 2 to 6 weeks.
† Maximal response in 2 to 8 weeks.
‡ Maximal response in 3 to 10 weeks.
§ No transfusion needed for 9 months to several years.
‖ Thrombocytopenia developed in 2 and persisted or became more marked in 5 patients.

patients. Hemorrhagic manifestations, noted clinically in four patients, contributed directly to the deaths of two patients. Splenomegaly, which recurred soon after the initial response to radiophosphorus, did not respond to additional P^{32}.

Figure 4 illustrates the course of a patient with chronic lymphocytic leukemia treated with radiophosphorus.

In summary, radiophosphorus was of significant benefit in five patients, of limited benefit in three, of transient benefit in two, and of no benefit in two.

C. *Polycythemia Vera:* Seven patients with polycythemia vera received P^{32} therapy. The survival of these patients ranged from 34 to 88 months after diagnosis, with a mean of 69 months (five and three quarters years). If the survival of these patients is related to the estimated date of onset, they survived from three and one-half to 15 years, with a mean survival of 113

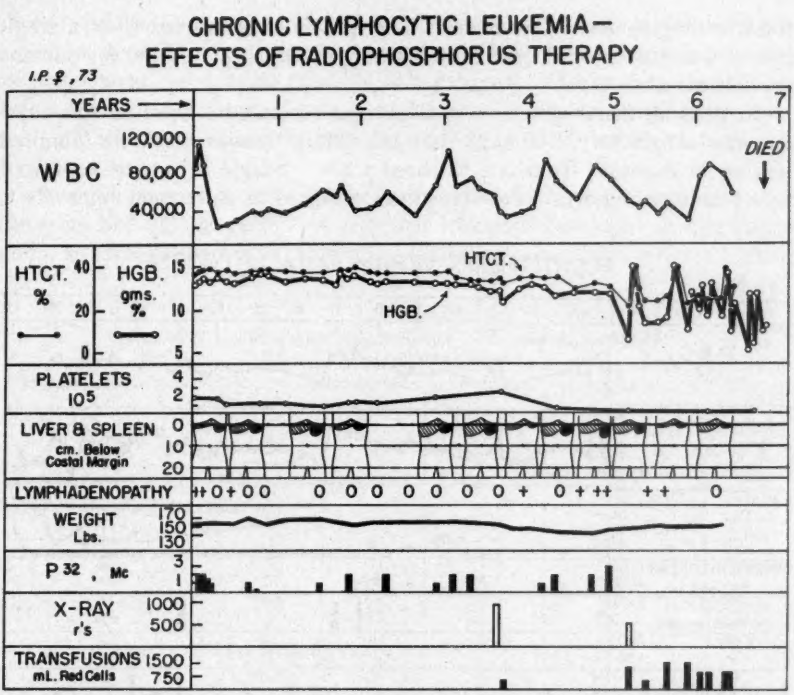

FIG. 4. Radioactive phosphorus therapy of chronic lymphocytic leukemia. Case 41, a 73 year old white woman with chronic lymphocytic leukemia, was treated with repeated injections of radioactive phosphorus over a five-year period. After an initial course of 6.4 mc. administered intravenously in doses of 2 mc. or less over an eight-week period the leukocyte count decreased to 22,000, moderate lymphadenopathy subsided completely, and weight increased. Splenomegaly and hepatomegaly were not influenced to any extent. Following this initial therapy the patient's disease was fairly well controlled for approximately four and one-half years with additional injections of P^{32} in doses ranging from 1 to 3 mc., given at one- to eight-month intervals. The leukocyte level was usually maintained between 40,000 and 65,000, with sporadic increases to over 100,000. Hemoglobin levels were maintained at suboptimal levels without transfusion. Splenomegaly and hepatomegaly persisted with only slight improvement. The patient then developed an anemia which required repeated transfusions. Thrombocytopenia became marked, hemorrhagic manifestations were prominent, lymphadenopathy recurred, and weight diminished. Splenomegaly did decrease after x-ray therapy to the spleen. However, the patient's course was progressively downhill and she died seven years after the diagnosis was established.

months (9.4 years) (table 3). Therapy during this period included venesection, phenylhydrazine, x-ray and radiophosphorus. Three patients had died and four were still alive at the end of this study. One died of subacute granulocytic leukemia and the other two died from unrelated diseases. Two patients were venesected before receiving P^{32}, four were venesected before and after P^{32} therapy, and one was treated extensively with phenylhydrazine, spray x-ray and venesection before receiving P^{32}.

Radiophosphorus was administered to patients with polycythemia vera

in doses ranging from 1 to 5 mc. The initial course varied from a single dose of 4 mc. to a total dose of 14.2 mc., given during a period of four and one-half months.

In general, the response to radiophosphorus administered in this manner was satisfactory. Clinical and laboratory remissions were obtained ranging in duration from one to three years. Single injections of 4 to 5 mc. of radiophosphorus were sometimes required at infrequent intervals to

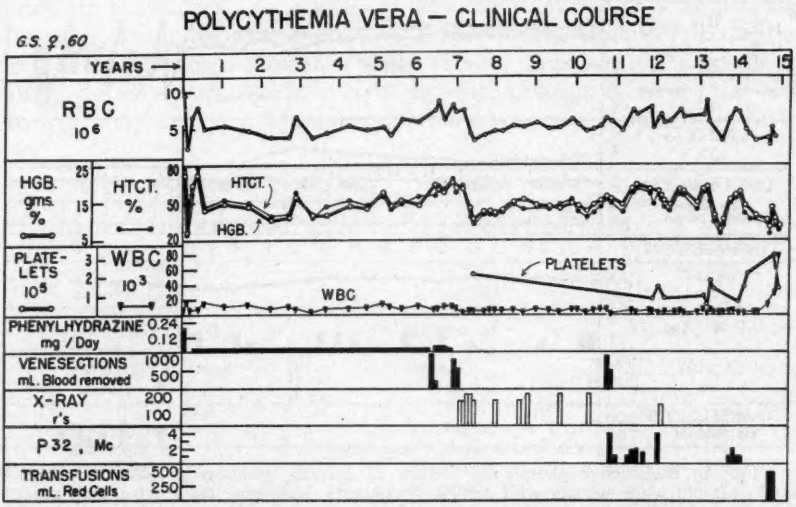

FIG. 5. Radioactive phosphorus therapy of polycythemia vera. Case 45, a 60 year old white female, presented a long history of polycythemia vera before radiophosphorus therapy was instituted. The patient's disease was satisfactorily controlled by phenylhydrazine for seven years. Venesections were then required to reduce the red cell count to approximately normal levels. Hematologic control was maintained by spray x-ray therapy for the ensuing four years. When x-ray therapy failed to control the polycythemia over a five-month period, radiophosphorus was given. Remissions of short duration (three to six months) were obtained. Leukopenia developed on each occasion, and a moderately severe anemia also occurred after the third course of P^{32}. After a fourth course of P^{32} a progressive increase in the white cell count was observed, anemia again developed, and the patient died 34 months after the initiation of P^{32} therapy. Autopsy revealed pathologic findings consistent with subacute granulocytic leukemia.

maintain control of the polycythemia. On occasions, larger total doses (7 to 12 mc.) were given in fractional amounts over a period of months.

The laboratory and clinical responses to radiophosphorus are summarized in table 4. It should be pointed out that one patient (case 45),* who died from subacute granulocytic leukemia, developed a severe anemia (figure 5). A severe refractory anemia occurred in another patient (case 48). Leukopenia, which developed in three patients, persisted for over one year

* This patient was referred by Dr. William B. Castle and Dr. T. Hale Ham, of Boston, who also kindly supplied detailed data summarizing her previous management.

in one patient, improved gradually in a second, and persisted in a third until an increase to 79,000 occurred terminally. There was a moderate decrease in platelets to the normal range in five patients. Hemorrhagic manifestation occurred only terminally in the patient who developed subacute leukemia. Marked splenomegaly and hepatomegaly also developed terminally in this patient.

In summary, radioactive phosphorus controlled the polycythemic process from one to five years. A terminal leukemia developed in one patient and a refractory anemia in a second. Leukopenia occurred in three patients

TABLE 3

Survival of Patients with Polycythemia Vera or Multiple Myeloma After Radiophosphorus Therapy

Case No.	Sex	Age	Total P^{32} (mc.)	Survival	
				From Onset (mos.)	From Diagnosis (mos.)
Polycythemia Vera					
43	F	57	16.0	87*	76
44	F	47	5.9	135	87‡
45	F	60	41.0	179*	34†
46	M	66	8.5	89*	88
47	M	63	26.0	66	58
48	F	57	23.4	154	77‡†
49	M	60	18.0	81	45‡
	Mean			113 (9.4 yrs.)	69 (5.75 yrs.)
Multiple Myeloma					
50	M	62	12.8	31	19
51	M	69	6.0	21	18
52	M	67	10.3	13	8
53	F	66	24.5	30	26
54	F	58	6.0	30	6
55	M	63	12.0	36	24
56	F	66	1.6	50	38
	Mean			30.1	19.8

* Died.

† Since initial treatment with radiophosphorus rather than since diagnosis. Diagnosis actually made 12 years previously for case 45 and 6 years previously for case 48.

‡ Last observation, 11/53.

and mild thrombocytopenia in four patients. Hemorrhagic and thrombotic complications were infrequent and mild.

D. *Multiple Myeloma:* Seven patients with multiple myeloma treated with radiophosphorus survived from six to 38 months after diagnosis (table 3). One patient who was alive 38 months after diagnosis (case 56) received only a single course of P^{32} (1.60 mc.), and urethane and cortisone were also used.

Radiophosphorus was administered in small doses, usually 2 to 2.5 mc.

The total initial course ranged from 1.60 to 12.8 mc., given over a period of from two days to three months.

In general, radioactive phosphorus was not an effective therapeutic agent in the treatment of multiple myeloma. Beneficial effects were limited to relief of bone pain in three patients. Destructive bone lesions remained unaltered on x-ray examination. A striking return to normal of the total protein and A/G ratio occurred in one patient, and there was partial improvement of a moderate anemia. Such beneficial effects were infrequent and of short duration. A more common finding was the development of a transient leukopenia. Thrombocytopenia developed after P^{32} in several patients. Bleeding phenomena were prominent throughout the illness of most of these patients, and very often assumed a major role terminally.

In summary, radioactive phosphorus appeared of little value in the treatment of multiple myeloma.

TABLE 4

Initial Clinical and Hematologic Response of Patients with Polycythemia Vera to Radiophosphorus Therapy

Clinical

1. Splenomegaly: present in 4 of 7 patients, decreased significantly in 3.
2. Hepatomegaly: present in 2 of 7 patients, decreased significantly in both.
3. Radiation sickness: none.
4. Thrombotic complications: infrequent, mild.
5. Hemorrhagic complications: infrequent, mild.

Hematologic

1. RBC, Hgb, Hct: maximal decline occurred in 2 to 5 months. Mild anemia developed in one patient, severe anemia in two patients.
2. WBC: significant decrease in WBC occurred in all 7 patients, maximal response after 1 to 4 months, usually by 2 months. Mild leukopenia occurred in 3 patients.
3. Platelets decreased to 100,000 to 250,000 in 5 of 7 patients. Already normal or moderately low in the remaining two patients.

E. *Hodgkin's Disease:* Four patients with Hodgkin's disease were treated with radioactive phosphorus. X-ray had previously controlled the disease for periods ranging from two to seven years. All patients were in relapse when P^{32} was first used, and probably were entering the terminal phase of their illness. Survival after P^{32} ranged from two weeks to one year, representing only a small fraction of the total survival time of each individual since the onset of the disease.

The beneficial effects of therapy were limited and transient. Lymphadenopathy decreased in three patients, the decrease being marked in one. Hepatomegaly and splenomegaly diminished in one. Pruritus was partially relieved in one patient, and general clinical improvement with an increase in appetite and weight occurred in another.

A persistent leukopenia and thrombocytopenia developed after radiophosphorus in one patient, and was transient but recurrent in another. Anemia developed in three patients, requiring transfusions. Marked depression of hematopoiesis occurred in two patients who received more intensive therapy.

In summary, radiophosphorus therapy in this small group of patients with Hodgkin's disease produced at best transient improvement in signs and symptoms in three patients. When given in the terminal phase of this illness, a dosage schedule sufficient to influence the pathologic manifestations of the disease also suppressed hematopoiesis.

F. *Acute Leukemia, Chronic Monocytic Leukemia, and Mycosis Fungoides:* Radiophosphorus was administered to eight patients with acute leukemia without any significant therapeutic response. Four patients survived only 11 to 28 days. The remaining four patients who also received cortisone therapy survived from three to five months.

One patient with chronic monocytic leukemia responded to an initial course of radioactive phosphorus in a manner similar to that observed in chronic granulocytic leukemia. Splenomegaly subsided completely, lymphadenopathy regressed, appetite improved, and the patient felt considerably better. The white cell count decreased from 110,000 to 3,500 one month after the patient received 10 mc. of P^{32}. This leukopenia was transient, and three weeks later the white cell count rose to 21,000. No further radiophosphorus was given to this patient. Further therapy included x-ray and blood transfusions. The patient died approximately 10 months after first being seen.

Two patients with mycosis fungoides received radioactive phosphorus. The beneficial effects consisted of slight but very transient relief of pruritus, with only minimal objective improvement of the skin lesions.

Discussion

Radioactive phosphorus in our experience has been an effective treatment for both chronic granulocytic and lymphocytic leukemia, and usually very effective in the control of polycythemia vera. Its beneficial effects in lymphomas and multiple myeloma were minimal, and acute leukemias did not respond to treatment with this agent. These conclusions are in essential agreement with the majority of opinions expressed in previous reports.[1-18]

With the exception of the series reported by Osgood et al.,[13-15, 30] radioactive phosphorus has not significantly prolonged survival of patients with either chronic granulocytic or lymphocytic leukemia. In a discussion of our survival data it should be pointed out that no effort was made to limit therapy to radiophosphorus. Other therapeutic agents and general supportive measures such as transfusions and antibiotics were used. With this reservation, the mean and median survival times of our patients with chronic granulocytic and lymphocytic leukemia from the onset of symptoms and from diagnosis are summarized in table 5.

The mean survival times of our patients with chronic leukemia may be compared with those obtained by other investigators who managed leukemia either without specific therapy or with x-ray, radioactive phosphorus or other agents (tables 6 and 7). Minot et al.[19] reported a mean survival from

date of onset of 3.04 years in a series of 52 patients with chronic granulocytic leukemia who received no specific therapy. Seventy-eight patients treated with irradiation survived an average period of three and one-half years. In another report by Minot and Isaacs,[20] 30 untreated chronic lymphocytic leukemia patients survived 3.3 years after the onset of their illness, while 50 patients treated by irradiation survived an average period of three and one-half years. The mean survival after onset in other series of patients treated by irradiation with x-ray, radiophosphorus or x-ray and radiophosphorus combined with chemical agents has ranged from two and one-

TABLE 5

Survival Time in Years for Patients with Chronic Leukemia

Series	Treatment	No.* Pts.	Arithmetic Mean		Median	
			From Onset	From Diagnosis† or Treatment	From Onset	From Diagnosis† or Treatment
I. Osgood [30]						
Granulocytic and lymphocytic combined	Titrated regularly spaced total body irradiation.	163 (47)	4.83	—	4.33	—
	Titrated irradiation to previously untreated patients.	100 (39)	4.86	—	4.83	2.60
II. Literature [29]						
Granulocytic and lymphocytic combined	Chiefly local x-ray	1978	—	—	2.65	—
	Conventional P^{32}	330	—	—	3.33	—
	Chiefly local x-ray	651	—	—	—	1.56
III. Chodos and Ross						
Granulocytic	P^{32} and local x-ray	30 (5)	2.50	1.82	2.30	1.66
Lymphocytic		12 (1)	4.25	2.85	3.75	2.50
Lymphocytic and granulocytic		42 (6)	3.03	2.11	2.50	1.79

* The figures in parentheses in this column represent the number of patients still living in each group.

† From diagnosis for the series of Chodos and Ross, and from treatment for the series of Osgood and the summary from the literature.

half to 4.83 years in chronic granulocytic leukemia,[2, 7, 10, 12–14, 21–25, 27, 30] and from 2.33 to 4.83 years in chronic lymphocytic leukemia.[2, 8, 11, 13–14, 22–28, 25–28, 30]

The limitation of expressing the survival in terms of an arithmetic mean has been discussed by Tivey [29] and Osgood et al.[15] This is illustrated by the skewed distribution obtained when the survival since onset of symptoms of our 42 patients with chronic leukemia is plotted on linear coördinates (figure 6A). It is obvious that the arithmetic mean of such a skewed distribution does not represent either the midpoint or the most probable value.

However, if the per cent survival is plotted against the logarithm of the survival time, a curve approaching normal (gaussian) distribution is obtained (figure 6B). The cumulative per cent dead since onset with respect to time, plotted on probability graph paper,* is summarized by figure 6C. Corresponding data for survival since diagnosis of these same patients are

TABLE 6

Chronic Granulocytic Leukemia: Summary of Representative Survival Data

Authors	Report Date	Treatment	No. Pts.	Mean Survival (Years)	
				From Onset	From Treatment or Diagnosis
Minot et al.[19]	1924	0	52	3.04	1.60
Minot et al.[19]	1924	Local radium	78	3.50	1.93
Hoffman and Craver [21]	1931	Local x-ray to spleen or to spleen and long bones	71*	3.36	2.62
Nathanson and Welch [23]	1937	Not given	123	3.33	—
Leavell [26]	1938	Irradiation and/or arsenic	87	3.20	—
Wintrobe and Hasenbush [22]	1939	Irradiation or potassium arsenite	23	2.79	1.68
Pascucci [27]	1942	Local irradiation	64	2.50	—
Reinhard et al.[2]	1946	P^{32} or P^{32} and x-ray. Fowler's solution to 8	39†	3.10	1.05
Lawrence et al.[7]	1948	P^{32} or P^{32} and x-ray	129	3.70	—
Friedell and Storaasli [10]	1949	X-ray and P^{32}	15	3.50‡	—
Diamond and Craver [12]	1951	X-ray and P^{32}. P^{32} and other agents	59	3.60	2.10§
Shimkin et al.[24]	1951	Irradiation and other agents	173‖	3.00	—
Osgood [13]	1951	Titrated irradiation	20	4.03	1.82
Osgood and Seaman [14]	1952	Titrated irradiation	163¶	>4.00**	—
Osgood [30]	1956	Titrated irradiation	163	4.83††	—

* Four long-lived patients excluded. Osgood has calculated total mean survival of 75 patients in this series to be 3.93 years.[13]

† Of the 39 patients, 21 had succumbed 3.54 years after onset of symptoms, and 0.84 years after treatment.

‡ Mean survival for 8 patients who died. Does not include 7 patients still living.

§ From first visit.

‖ Of the 173 patients, 131 received irradiation; 22, irradiation plus chemical agents; 10, chemical agents; 20, no treatment.

¶ Includes both chronic granulocytic (61) and lymphocytic (102) leukemia patients treated with P^{32} (140) or x-ray (23).

** Seventy-three of 163 patients still alive. Estimated final mean survival for 163 patients was 7.0 years.

†† Forty-seven patients still alive, so estimated mean survival is considerably longer—6.66 years.

represented in figure 7. The median survival, which represents the time when 50% of the patients are dead, may be read directly from curve 6C and 7C.

The mean and median survival of our patients may be compared with that reported by Osgood [30] for patients with chronic leukemia treated by titrated, regularly spaced irradiation with P^{32} or x-ray (table 5). Survival

* Keuffel & Esser Co. probability scale graph paper No. 358-23.

data from the literature for chronic leukemia patients treated chiefly by local x-ray, and for patients treated chiefly by P^{32} given in a conventional manner, are also included in table 5. The survival figures obtained by Osgood are significantly better than those of any other series reported in the literature, including those in the present report.

In our treatment of patients with chronic leukemia, the quantity of P^{32} administered in the initial course depends upon the disease being treated, the route of administration, the degree of elevation of the leukocyte count,

TABLE 7

Chronic Lymphocytic Leukemia: Summary of Representative Survival Data

Authors	Report Date	Treatment	No. Pts.	Mean Survival (Years)	
				From Onset	From Treatment or Diagnosis
Minot and Isaacs [20]	1924	0	30	3.33	1.93
	1924	Local radium	50	3.53	2.08
Nathanson and Welch [23]	1937	Not given	64	3.33	—
Leavell [25]	1938	Irradiation and/or arsenic	49	3.60	—
Wintrobe and Hasenbush [22]	1939	Irradiation or potassium arsenite	23	2.33	1.07
Bethell [26]	1942	Local x-ray to spleen or long bones	18	4.38	1.95
Pascucci [27]	1942	Local irradiation	64	2.80	—
Reinhard et al.[2]	1946	P^{32} or P^{32} and x-ray	30*	2.53	0.93
Lawrence et al.[8]	1949	P^{32} or P^{32} and x-ray	97	4.50	—
Diamond et al.[11]	1950	X-ray and P^{32}, P^{32} and other agents	53	4.20	2.40
Osgood [13]	1951	Titrated irradiation	38	3.36	1.33
Osgood and Seaman [14]	1952	Titrated irradiation	163†	>4.00‡	—
Shimkin et al.[28]	1953	Irradiation and other treatment	137§	3.50	—
Osgood [30]	1956	Titrated irradiation	163	4.83‖	—

* Of the 30 patients, 15 were dead 2.30 years after onset of symptoms, 14 were still living.

† Includes both chronic granulocytic (61) and lymphocytic (102) leukemia treated with P^{32} (140) or x-ray (23).

‡ Seventy-three of 163 patients still alive. Estimated final mean survival for 163 patients was 7.0 years.

§ Of the 137 patients, 96 received irradiation; 18, irradiation and chemical agents; 8, chemical agents; 15, no treatment.

‖ Forty-seven of 163 patients still alive, so estimated mean survival is considerably greater, viz., 6.66 years.

and the size of the spleen and lymph glands. No effort is made to calculate the dose precisely on the basis of the patient's weight, although this factor is taken into consideration. A larger initial course is usually employed in chronic granulocytic leukemia (10 to 12 mc.) than in chronic lymphocytic leukemia (6 to 8 mc.). The P^{32} is usually administered intravenously in 1 to 4 mc. doses at one- to seven-day intervals. If orally administered, the estimated intravenous dose is multiplied by the factor 5/4.

After treatment has been started, patients are evaluated at intervals of from one to two months. If there is evidence of progression of their dis-

ease, 1 to 5 mc. doses of P^{32} are given in an effort to maintain the leukocyte count in the range of 15,000 to 30,000 and the patient in clinical remission. The quantity of P^{32} administered is dependent upon the type of leukemia, the previous response of the patient and the severity of the relapse. Caution is indicated, particularly if thrombocytopenia developed after previous radio-

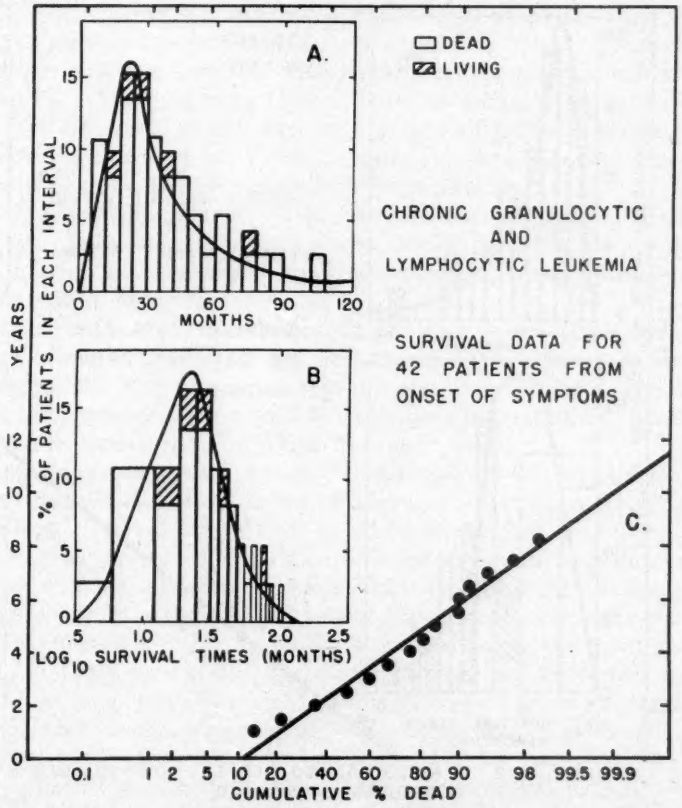

FIG. 6. Distribution of total survival time from onset of symptoms of 42 patients with chronic leukemia (granulocytic and lymphocytic) treated with P^{32}. Some patients received x-ray therapy before, or after, treatment with P^{32}. Curve A: skewed distribution when survival data are plotted against time; Curve B: normal distribution achieved when same survival data are plotted against logarithm of survival time; Curve C: cumulative per cent of patients dead in relation to time.

phosphorus treatment. Smaller doses are required for maintenance in chronic lymphocytic leukemia than in chronic granulocytic leukemia.

The response to successive courses of therapy may decrease progressively in degree and duration. Hepatomegaly, splenomegaly and lymphadenopathy may remain unchanged for prolonged periods, although hematologic

improvement may continue to occur. Therapy need not be limited to P^{32}, and x-ray therapy to the spleen and lymph glands is administered if these organs enlarge progressively and fail to respond to P^{32}. Patients will frequently respond to x-ray treatment after failing to respond to the usual dose of P^{32}. As a general rule, however, remissions after x-ray, or P^{32} adminis-

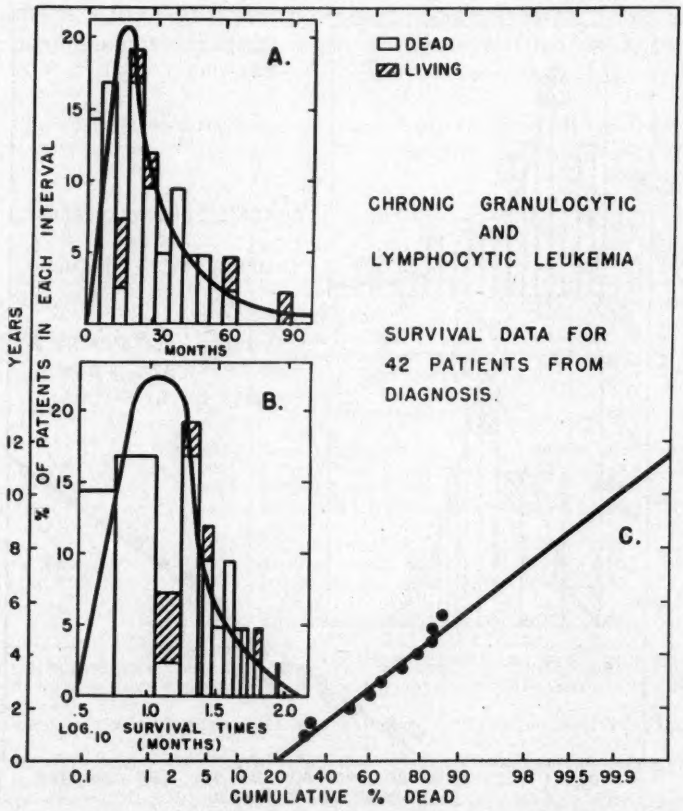

FIG. 7. Distribution of total survival time since diagnosis of 42 patients with chronic leukemia (granulocytic and lymphocytic). Some patients received x-ray therapy before or after P^{32}. Curves A, B and C are plotted as in figure 6.

tration during the later stages of these diseases become progressively shorter as the patient becomes refractory to all therapy.

There are obvious hazards in the use of radiophosphorus in the treatment of leukemia.[31] Thrombocytopenia, which may occur naturally in chronic leukemia and particularly in lymphocytic leukemia, may first appear or progress following radiophosphorus therapy. Ultimately, thrombocytopenia or pancytopenia of a severe and even fatal degree may occur after pro-

longed P^{32} therapy. These hematologic complications represent the effect of overdosage and can usually be avoided by careful adjustment of the dose in relation to the clinical course of the patient. On the other hand, the development of an acute blastic leukemia during the terminal stages of chronic granulocytic or lymphocytic leukemia may not be necessarily the result of radiation therapy. A blastic type of leukemia occurred as a terminal event in 16% of our patients with chronic granulocytic leukemia, while the incidence in the literature has ranged from 25 to 33%.[7, 12, 14] The incidence of terminal blastic leukemia is considerably less in patients with chronic lymphocytic leukemia, ranging from none in our series to 7% in the literature.[8, 11, 14] Wiseman et al.[17] have stated, without giving supporting data or references, that terminal acute leukemia has been observed more frequently in radiation-treated cases of chronic leukemia.

Despite these hazards, P^{32} is effective in the management of chronic leukemias. It has the advantages of ease of administration, it rarely produces radiation sickness, and it can be given with minimal discomfort and inconvenience to the patient.

Because of these advantages, and its efficiency in producing remissions in polycythemia vera, many investigators consider P^{32} therapy the treatment of choice in the management of this disorder.[4, 5, 6, 9, 10, 17, 32] The disadvantages attributed to other conventional methods of treatment of polycythemia have been summarized by Wiseman et al.[17]

The therapeutic regimen used for the management of polycythemia vera has been described under "Results of Therapy." Treatment is again individualized. The initial total dose in our experience may vary from 2 to 8 mc., given over a period of from one to two weeks in individual doses ranging from 1 to 5 mc. Further P^{32} administration is delayed for at least eight weeks after the initial course. This delay is necessary because the maximal inhibitory effect of P^{32} on erythropoiesis cannot be evaluated until most of the red blood cells present during the initial course have lived their normal life span and have been destroyed. If this precaution is observed, anemia, leukopenia and thrombocytopenia are less likely to develop as complications of therapy.

Polycythemia vera may be successfully controlled for long periods of time by radiophosphorus. Remissions may be obtained with minimal discomfort to the patient and may last an average of 18 to 24 months, with a range of from six months to six years.[33] Venesection is necessary initially if rapid control of the disease is indicated to prevent thrombotic complications.

The major objection advanced against the use of radiophosphorus as the treatment of choice for polycythemia vera has been the hazard of administering internal radiation to individuals with a chronic disease. The long-term effects of internally administered radiophosphorus have not been fully evaluated. It is well known, however, that chronic granulocytic leukemia

may develop as a terminal complication of polycythemia vera in 10 to 12% of the cases [33, 34] treated by conventional means. Since the advent of P^{32} therapy, Lawrence [9] has reported five cases of terminal leukemia in 119 polycythemia vera patients, or an incidence of 4%. Erf [4] reported five cases in 214 patients with polycythemia vera, or an incidence of 2.2%. These figures may be compared with those reported by Tinney et al.,[34] who observed an incidence of terminal leukemia in 10% (17 of 163) of patients treated by venesection.

It would appear that radiation therapy with P^{32} has not increased the occurrence of chronic granulocytic leukemia in patients with polycythemia vera. There is suggestive evidence that the incidence of acute leukemia is greater now than in the days before treatment with radiophosphorus. Stroebel and Hall,[33] in a series of 170 cases, observed the development of fulminating acute leukemia without preceding chronic granulocytic leukemia on four occasions. On one occasion, acute leukemia developed in a patient known to have granulocytic leukemia. Wiseman et al.[17] have summarized the causes of death in 453 cases of polycythemia vera treated with P^{32} in various clinics and found 12 of 40 deaths to be due to acute leukemia. This is an incidence of acute leukemia of 2.7% for the entire series, but it is actually 30% of those who died. Stroebel, Hall and Pease [18] report four deaths from acute leukemia in a group of 32 patients with polycythemia vera who died after receiving therapy other than P^{32}. In a more recent report Stroebel [35] states that eight (3.3%) of 241 patients with polycythemia vera treated with P^{32} died from acute leukemia. Nine patients died of "anemia with leukemoid reactions," 15 were alive with "anemia with leukemoid reactions," and one developed a transitory hypoplastic anemia. This represents 32 of 241 patients (13.2%) with serious hematologic complications.

In our own small series of seven patients, subacute leukemia did occur terminally in a single case. This patient had been treated with phenylhydrazine, venesection and spray irradiation, as well as with P^{32}. Final evaluation of this possible complication of P^{32} therapy will require a larger number of cases than have yet been reported. At present, however, the evidence is not sufficiently clear-cut to outweigh the advantages of this form of therapy in the treatment of polycythemia vera.

Summary and Conclusions

1. Radioactive phosphorus is an effective agent in the management of chronic granulocytic leukemia, chronic lymphocytic leukemia and polycythemia vera. It was not of any significant benefit in Hodgkin's disease, multiple myeloma, acute leukemia and mycosis fungoides.

2. The advantages of radiophosphorus include ease of administration, the infrequency of radiation sickness, and the fact that it can be given with minimal inconvenience to the patient.

3. Patients treated with radiophosphorus survive approximately as long as those treated by other agents. However, the survival of patients in the

present series who were treated intermittently with radiophosphorus was significantly less than that obtained by Osgood with continuous titrated irradiation.

4. The program of therapy used for each condition has been presented. Treatment in leukemia is individualized. Dosage is dependent upon the type of leukemia, its current status and the response of the individual patient. Supplementary therapy with x-ray is used if needed to reduce splenomegaly or lymphadenopathy. Supportive therapy with blood, antibiotics and steroids is used as required.

5. Radiophosphorus treatment of polycythemia vera likewise is individualized. Initial or supplementary venesection, x-ray therapy or other treatment may be required in individual cases.

6. Leukopenia, thrombocytopenia and perhaps acute blastic leukemia may occur after P^{32} treatment of the chronic leukemias, particularly the granulocytic forms. Terminal leukemia has also been observed in polycythemia vera. The incidence of this latter complication probably does not exceed that encountered in polycythemia vera treated by other methods. These hazards of radiophosphorus therapy must be considered whenever radiophosphorus is administered.

Summario in Interlingua

Phosphoro radioactive es hodie generalmente acceptate como un efficace agente therapeutic pro leucemia chronic e polycythemia ver. Tamen, il existe un certe disaccordo de opinion quanto al melior maniera de su uso in le tractamento de patientes con leucemia chronic. In le majoritate del clinicas, le therapia esseva initiate per le methodo "fractional" o "saturational." Administrationes additional de radiophosphoro es usate solmente quando un progresso ulterior del morbo es evidente. Le periodo de superviventia assi effectuate ha essite approximativemente illo obtenite per medio de therapia a radios X.

Recentemente Osgood ha attaccate iste conception. Ille ha presentate datos que pare indicar que un continue therapia titrate con radios X o con radiophosphoro es plus efficace in prolongar le vita del patiente con leucemia chronic e in render su vita plus confortabile e utile.

Le presente reporto summarisa nostre decenne experientia con phosphoro radioactive in le tractamento clinic de 71 patientes con leucemia, lymphoma, o polycythemia ver. Le methodologia therapeutic dependeva del responsa clinic e hematologic del patiente individual. Phosphoro radioactive esseva administrate solmente in casos in que le progresso del morbo esseva evidente. Esseva facite nulle effortio a restringer le tractamento al uso de radiophosphoro.

In nostre experientia, phosphoro radioactive se ha monstrate efficace in le tractamento de chronic leucemia granulocytic e de chronic leucemia lymphocytic. Usualmente illo esseva multo efficace in le control de polycythemia ver. Su effectos benefic in lymphomas e in myeloma multiple esseva minimal, e leucemias acute non respondeva al tractamento con iste agente.

Le periodo medie de superviventia a partir del declaration del symptomas esseva 3,03 annos pro le 42 patientes con leucemia chronic in le presente serie. Iste total de 42 includeva 30 chronic casos granulocytic e 12 chronic casos lymphocytic. Le periodo median de superviventia in iste gruppo esseva duo annos e medie. Le periodos medie e median del superviventia a partir del diagnose o a partir del prime tractamento in iste mesme serie de patientes esseva 2,11 e 1,79 annos respectivemente.

Iste periodos de superviventia es significativemente inferior a illos obtenite per Osgood con titrate, regularmente intervallate irradiationes del corpore total (per radios X o radiophosphoro). Osgood ha reportate periodos medie e median a partir del declaration del symptomas de 4,83 e 5,33 annos, respectivemente, pro 163 patientes con leucemia chronic. Cento patientes de Osgood habeva un periodo median de superviventia a partir del diagnose de 2,6 annos.

Le avantages de radiophosphoro in le tractamento de leucemia chronic e de polycythemia ver include le facilitate del administration, le infrequentia de morbo de irradiation, e un minimo de disconforto pro le patiente.

Leucopenia, thrombocytopenia, e forsan acute leucemia blastic pote occurrer post le administration de radiophosphoro in le tractamento de leucemia chronic. Etiam leucemia terminal ha essite observate post therapia a P^{32} pro polycythemia ver. Le incidentia de iste ultime complication non excede, probabilemente, illo incontrate in casos de polycythemia ver tractate per altere methodos. Omne iste riscos debe esser prendite in consideration quandocunque radiophosphoro es administrate.

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POLYCYTHEMIA WITH PAPILLEDEMA AND INFRATENTORIAL VASCULAR TUMORS *

By GRIER F. STARR, M.D., CHARLES F. STROEBEL, JR., M.D., F.A.C.P., and THOMAS P. KEARNS, M.D., *Rochester, Minnesota*

INFRATENTORIAL vascular tumors have been noted in association with polycythemia by several authors, although the true incidence of this association is conjectural. Few reports have presented adequate hematologic data. Reëmphasis of the diagnostic problem presented by patients with polycythemia and papilledema appeared justified. It was therefore thought advisable to examine the experience at the Mayo Clinic with infratentorial vascular tumors and their association with polycythemia and papilledema.

PRESENT STUDY

The clinical records of all patients with infratentorial vascular tumors were reviewed and microscopic sections of these tumors were examined. No tumor was accepted without histologic verification. Special staining procedures, including the Perdrau technic, Mallory's phosphotungstic acid-hematoxylin, van Gieson's and fat stains, were used in addition to routine staining with hematoxylin and eosin.

A total of 106 infratentorial vascular tumors were found in the surgical and necropsy files. Of these tumors, 97 involved the cerebellum; of the remainder, one was said to arise from the medulla, four from the "fourth ventricle" and one from the foramen magnum, whereas three were designated simply as "infratentorial."

The tumors were classified into three histologic groups, essentially following the scheme of Turner and Kernohan.[1] One group of tumors resembled cavernous hemangiomas occurring elsewhere in the body and were designated as such. These lesions, 14 in number, were considered as congenital anomalies or hamartomas. A second group of tumors were considered to be hemangio-endotheliomas. These made up the bulk of the lesions, 90 in number. They resembled capillary hemangiomas, exhibiting endothelium-lined spaces and varying amounts of stroma. Larger cells containing fat demonstrable by special stains frequently were seen and appeared to be related to the amount of necrosis and hemorrhage within the tumor. The remaining two lesions exhibited pronounced pleomorphism,

* Received for publication August 26, 1957.

From the Sections of Surgical Pathology, Medicine and Ophthalmology, Mayo Clinic and Mayo Foundation.

The Mayo Foundation, Rochester, Minnesota, is a part of the Graduate School of the University of Minnesota.

Requests for reprints should be addressed to Section of Publications, Mayo Clinic, Rochester, Minnesota.

giant cells and occasional mitotic figures. They were classified as hemangioblastomas, although they did not differ clinically from hemangio-endotheliomas. Angiosarcomas were not seen.

Of these 106 patients, 38 (36%) had values for hemoglobin greater than 15 gm. per 100 ml. of blood. Eleven of these 38 patients had hemoglobin values greater than 18 gm. Four of these 11 had determinations of blood volume.

Case Reports

Table 1 illustrates data in seven of the 11 patients who had hemangioendotheliomas and hemoglobin values of more than 18 gm., suggestive of polycythemia. In three patients the hemoglobin decreased to normal after operation, suggesting a cause-and-effect relationship with the tumor. Postoperative values for hemoglobin were not recorded in the other four instances. The type of polycythemia was not known in these seven cases because of insufficient hematologic data. The amount of dehydration was not apparent in the records, although most of the patients had experienced some vomiting; however, the leukocyte counts in the five patients who had preoperative determinations were not increased, as one would expect with hemoconcentration resulting from dehydration.

The following case reports represent the four afore-mentioned patients on whom determinations of blood volume were done.

*Case 8.** A 53 year old white man was seen at the Mayo Clinic in September, 1953. A year previously the hemoglobin had been normal. Two months prior to admission he had begun to have headaches. Four weeks later the hemoglobin measured 20 gm. and the erythrocyte count was 6,520,000 cells per cubic millimeter of blood. Three phlebotomies were done in the four weeks preceding admission to the clinic; 500 ml. of blood were removed on each occasion.

Examination at the clinic disclosed a hemoglobin of 16.4 gm. and a value for packed cells (hematocrit) of 51%; the leukocyte count was 6,300. The total blood volume was 5,937 ml. (72 ml. per kilogram of body weight), with a plasma volume of 2,909 ml. (35 ml./kg.) and an erythrocytic volume of 3,028 ml. (37 ml./kg.). Papilledema of one diopter on the right and two diopters on the left was noted.

Suboccipital craniotomy was done and a solid hemangio-endothelioma was partially removed from the right cerebellar hemisphere. The tumor filled the fourth ventricle and extended into the spinal cord to the level of the second cervical vertebra. A Torkildsen procedure was performed. Postoperative roentgen therapy was administered. Hemoglobin values after operation varied from 14 to 15.5 gm. The patient was alive but his condition was unknown two years after operation.

Case 9. A 53 year old white man came to the clinic in January, 1943, with a chief complaint of progressively severe headaches and loss of balance since May, 1942. In September, 1942, his hemoglobin had measured 20 gm., with an erythrocyte count of 5,650,000 and a leukocyte count of 6,960.

Examination revealed papilledema of three diopters on the right and two on the left. The hematocrit value was 58%. Total blood volume was 5,964 ml. (69 ml./kg.), with a total plasma volume of 2,684 ml. (31 ml./kg.) and an erythrocytic volume of 3,280 ml. (38 ml./kg.). Medical treatment was instituted because of the possibility of an inflammatory lesion of the brain.

* Reported in part by Kearns.[2]

TABLE 1

Data in Seven Patients with Hemoglobin of More Than 18 Gm.

Case	Age (yr.), Sex	Preoperative Values				Postoperative Values				Papilledema	Tumor	Comment
		Hemoglobin (gm.)	RBC	WBC	Hematocrit, %	Hemoglobin (gm.)	RBC	WBC	Hematocrit, %			
1	40 M	18.2	4.91	6,900	—	—	—	—	—	Present	Cystic hemangio-endothelioma, rt. cerebellum	Died first postop. day
2	55 M	18.5	—	9,400	—	—	—	—	—	Present	Solid friable hemangio-endothelioma, lt. cerebellum	Alive and well 18 years postop.
3	61 M	18.7	5.39	—	59	15	—	5,500	51	Present	Cystic and solid hemangio-endothelioma, lt. cerebellum	No follow-up
4	33 F	20.8	5.44	4,400	—	12.4	4.5	9,900	—	Absent; herniation of cerebellum through old operative site	Cystic and solid hemangio-endothelioma, rt. cerebellum	Died 16 days postop.; 10 yrs. previously, a cystic hemangio-endothelioma had been removed elsewhere
5	16 M	20.8	6.47	—	62	—	—	—	—	Present	Cystic hemangio-endothelioma, lt. cerebellum	Died 9 mo. postop. Suggestive family history compatible with Lindau's disease
6	25 M	18.3	—	9,000	—	14.6	5.0	9,400	—	Present	Cystic hemangio-endothelioma, rt. cerebellum	Well 13 years postop.
7	17 M	19.1	—	6,600	—	—	—	—	—	Present	Solid hemangio-endothelioma, fourth ventricle	Died second postop. day

The patient returned four months later with increased papilledema, dizziness and diplopia. Ventriculography was done, followed by suboccipital craniotomy. The hemoglobin at that time was 18.9 gm. A large cystic hemangio-endothelioma, essentially in the midline but arising from the left cerebellar hemisphere, was removed completely. Postoperative studies showed a hemoglobin of 15.9 gm., erythrocytes numbering 4,530,000 and a leukocyte count of 8,600; the hematocrit value was 48%. The patient was asymptomatic five years later but subsequently was lost to follow-up.

These two cases represent mild relative polycythemia, according to the blood volume studies (erythrocytic volumes of 37 ml./kg. and 38 ml./kg., respectively). The phlebotomies just prior to admission in case 8 probably altered the hematologic picture somewhat.

Case 10. A 45 year old white man came to the clinic in May, 1930, because of failing vision, vomiting, insomnia, ataxia and headaches. Examination revealed bilateral papilledema of three to four diopters and coarse tremor of the hands. The hemoglobin measured 16.9 gm. and erythrocytes numbered 5,270,000. Operation disclosed a hemangio-endothelioma of the left cerebellar hemisphere, both solid and cystic in nature, that also involved the fourth ventricle. Decompression without removal of the tumor was done because of excessive bleeding. Postoperative external radium therapy was given, followed by roentgen therapy.

The patient returned in June, 1931, with vertigo, blurred vision, and impaired speech and memory. The hemoglobin at that time was 13.7 gm., with an erythrocytic count of 4,700,000 and leukocytes numbering 5,900. Roentgen therapy produced some amelioration of symptoms. Subsequent values for hemoglobin were 17.5 gm. in August, 1932, and 17.4 gm. in July, 1935.

The patient returned in 1936. His hemoglobin was 18.8 gm.; erythrocytes numbered 5,290,000 and the leukocyte count was 4,500. He had become much worse in the two weeks before admission, with weakness, incoördination, inability to walk and projectile vomiting. Roentgen therapy was given for six weeks, without relief. The hemoglobin increased to 20.9 gm., with a hematocrit value of 63%. Total blood volume was 6,919 ml. (86 ml./kg.), with a total plasma volume of 2,560 ml. (32 ml./kg.) and an erythrocytic volume of 4,359 ml. (54 ml./kg.). Suboccipital craniotomy was done, with subtotal removal of the tumor, which was primarily in the midline and involved both cerebellar lobes. The lesion apparently was solid, no cystic component being noted. The patient had an undulating blood pressure postoperatively and died later that day.

This patient's hematologic picture is suggestive of absolute secondary polycythemia. The erythrocytic volume was 54 ml./kg., whereas the normal value is considered to be 40 to 50 ml./kg. using a dye technic, either Congo red or Evans blue. Values of 50 to 60 ml./kg. are considered to be borderline, probably polycythemic, and values of 60 ml./kg. or more are considered definitely polycythemic.[3]

*Case 11.** A 35 year old man, a taxi driver, came to the clinic in October, 1945, complaining of headaches, vomiting and attacks of vertigo that had been gradually progressive for nine months. Neurologic evaluation showed no focal signs, but bilateral papilledema and engorgement of the retinal veins were noted. The blood pressure was normal, and the spleen was not palpable. Roentgenograms of the head and thorax showed nothing abnormal. Five phlebotomies gave no relief of symp-

* Reported in part by Stroebel and Fowler.[4]

toms, and the papilledema progressively increased. The various hematologic data are summarized in table 2.

Ventriculography was done, followed by suboccipital craniotomy, with exploration of the subtentorial region. A right cerebellar hemangio-endothelioma was encountered and partially removed. Postoperatively, four roentgen treatments were given to this region; 25 subsequent roentgen treatments were given elsewhere in March and June, 1946.

The patient was reëxamined at the clinic in July, 1947. He had improved and returned to work. Results of neurologic examination were essentially normal and papilledema was absent.

TABLE 2

Chronologic Hematologic Data: Case 11

10-27-45	Hemoglobin, 22.3 gm.; hematocrit, 76%
10-30-45	Hemoglobin, 21.5 gm.; RBC, 7,280,000; hematocrit, 68%
11-2-45	Total blood volume, 6,765 ml. (125 ml./kg.) Total plasma volume, 1,962 ml. (36 ml./kg.) Erythrocytic volume, 89 ml./kg.
11-3-45 to 11-9-45	Five phlebotomies (each 500 ml.)
11-10-45	Hemoglobin, 16.6 gm.; RBC, 4,160,000; hematocrit, 59%
11-14-45	Total blood volume, 5,225 ml. (98 ml./kg.) Total plasma volume, 2,665 ml. (50 ml./kg.) Erythrocytic volume, 48 ml./kg.
11-20-45	Subtotal removal of right cerebellar hemangio-endothelioma
11-26-45	Total whole blood volume, 4,569 ml. (89 ml./kg.) Total plasma volume, 2,879 ml. (56 ml./kg.) Erythrocytic volume, 33 ml./kg.
11-27-45	Hemoglobin, 11.6 gm.; RBC, 3,900,000; WBC, 7,800; hematocrit, 38%
11-30-45	Hemoglobin, 13.0 gm.; RBC, 4,330,000; WBC, 7,200; hematocrit, 42%
7-28-47	Hemoglobin, 16.6 gm.; RBC, 5,800,000; WBC, 5,700
1-24-52	Hemoglobin, 17.6 gm.; RBC, 6,100,000; WBC, 5,400
1-25-52	Total blood volume, 6,227 ml. (88 ml./kg.) Total plasma volume, 2,055 ml. (29 ml./kg.) Erythrocytic volume, 59 ml./kg.
1-26-52 to 1-29-52	Three phlebotomies (each 500 ml.)
5-16-52	Hemoglobin, 18.0 gm.; RBC, 5,200,000; WBC, 6,700; hematocrit, 56%
5-17-52 and 5-20-52	Phlebotomies (500 ml.) on each date
5-26-52	Suboccipital craniotomy with exploration and Torkildsen procedure
6-3-52	Hemoglobin, 14.9 gm.; RBC, 5,010,000; WBC, 4,700; hematocrit, 47%

The patient returned again in January, 1952. Neurologic examination again showed nothing abnormal; however, he had noted headaches of progressing severity for the previous six months. Roentgen therapy was recommended, and 20 treatments were given. Three phlebotomies (500 ml. each) were also done. The headaches were not relieved, and the patient began noticing difficulty in walking. He occasionally would vomit on arising from bed in the morning.

In May, 1952, cerebellar signs were noted on examination, and a suggestion of recurrent papilledema was present. Two additional phlebotomies were done, with no effect. Therefore, reëxploration of the suboccipital region was done. This revealed adhesions thought to be producing obstruction to the flow of cerebrospinal fluid, but residual tumor was not encountered.

A Torkildsen procedure (right ventriculocisternostomy) was done to relieve increased intraventricular pressure. A letter in July, 1953, reported the patient to be relatively well and continuing as a dispatcher for the taxi company.

The preoperative erythrocytic volume in 1945 and that in 1952 were in the range of absolute polycythemia. This patient had recurrence of polycythemia apparently resulting from adhesions producing internal hydrocephalus. Residual tumor was not found. This is a most significant observation, and tends to refute the theory that erythropoiesis occurs in these vascular tumors themselves.

Comment

Polycythemia may be divided into an absolute type (polycythemia vera and secondary polycythemia) and a relative form. Absolute polycythemia is present if the erythrocytic volume, inferred from plasma dye studies or use of albumin-tagged radioiodine, exceeds 60 ml. per kilogram, the normal being 40 to 50 ml., as already stated. Different normal values are used if the erythrocytic volume is determined by the direct tagging of erythrocytes by radiochromium, which gives a normal range between 25 and 38 ml. per kilogram. As mentioned previously, an inferred erythrocytic volume of 50 to 60 ml. is equivocal but is suggestive of absolute polycythemia and may be significant in the presence of splenomegaly or leukocytic abnormalities. Increased hemoglobin and hematocrit values and morphologic changes in the granulocytic cells, with or without splenomegaly, may be considered to be diagnostic of absolute polycythemia with little fear of error, even in the absence of determinations of blood volume.

Of the cases in our series, four may be classified on the basis of blood-volume determinations. Case 11 is an example of absolute secondary polycythemia, and case 10, although borderline, most probably is an example. Cases 8 and 9 are instances of relative polycythemia. The remaining seven cases support the association between these tumors, evidence of increased intracranial pressure and polycythemia. In these, as in most reported cases, insufficient data are present for accurate classification, a most unsatisfactory situation that is rationalized by the realization that these patients often were acutely ill and that such apparently academic procedures were considered ill-advised in the immediate management of the patient.

Significant splenomegaly was not detected in any of these 11 cases, which is consistent with previously reported experience.

Polycythemia vera with manifestations in the central nervous system, especially papilledema, must be considered in the differential diagnosis of these lesions. Polycythemia vera produced symptoms associated with the central nervous system in 127 (78%) of the 163 cases reported by Tinney and associates;[5] papilledema was present in four of these 127 patients. Drew and Grant[6] found reports of 17 cases of polycythemia vera with papilledema. It is often difficult to determine clinically whether papilledema

has resulted from polycythemia vera or whether both the papilledema and the polycythemia are the result of a tumor in the posterior fossa. When faced with a patient who has polycythemia and papilledema, the clinician must be aware of the triad of polycythemia, papilledema and posterior-fossa hemangio-endothelioma. The presence of such a tumor should be excluded before it is assumed that the papilledema results from polycythemia alone. Phlebotomy usually produces clinical improvement and subsidence of the papilledema in the patients with polycythemia vera, unless damage to the brain has occurred from hemorrhage or thrombosis. Patients who have cerebellar vascular tumors should not be significantly benefited by this procedure.

Pathologically, one must distinguish between hemangio-endothelioma of the cerebellum and metastatic hypernephroma. This distinction occasionally may be impossible until the possibility of a renal lesion has been definitely excluded. It must be remembered that cysts and hypernephromas of the kidneys are seen in Lindau's [7] disease, and critical evaluation of such cases is necessary to avoid confusion.

We have been able to find 26 reported cases of polycythemia or erythrocytosis associated with infratentorial vascular tumors.[8-20] Studies of the blood volume were included in only three of these.[8, 17] In a fourth case a postoperative decrease of the erythrocytic volume was mentioned but figures were not given.[16] Ward and co-workers [17] did not convert their figures for the erythrocytic volume to milliliters per kilogram; if this is done, assuming the patients were of average weight, their case 2 is an example of relative polycythemia. Carpenter and associates [8] reported one case with blood volume determinations compatible with absolute secondary polycythemia. As a result of blood volume determinations, we are adding one case of absolute secondary polycythemia, one case of borderline absolute secondary polycythemia, and two cases of relative polycythemia.

The mechanism of production of polycythemia in patients with these tumors is not known. That such an association exists is supported by the fact that the hematologic findings became normal in six of our 11 patients after operation. Three of the remaining patients died in the immediate postoperative period and data are therefore not available. A similar return to normal of the hemoglobin and erythrocyte counts was present [8, 13, 14, 16-20] in 15 of the 26 cases in the literature. Neurologic conditions other than infratentorial vascular tumors have been described as being associated with polycythemia.[6, 8, 21-23] Although anatomic evidence was not always presented, there is a suggestion that a lesion affecting the mesodiencephalic region is a common feature. The effect of cerebellar hemangio-endotheliomas on the diencephalon was not immediately apparent. All the patients reported on in the literature and all but one of our patients showed papilledema. In this exception (case 4, table 1), herniation of the cerebellum through the old operative site was present. Some authors [8, 22, 23] thought

that a pronounced increase in intraventricular pressure affects either a postulated mesodiencephalic erythropoietic center or the regulatory centers for water balance, or both. Holmes and associates [10] considered that the primary stimulus for the polycythemia is relative anoxia caused by depression of the medullary centers for a prolonged period due to a slowly growing tumor producing increased intracranial pressure. They reported two cases with oxygen-capacity studies to support this view.

Although definite conclusions are not available as yet, it would appear on the basis of our case 11 and other cases reported by Holmes and coworkers that either a center affecting water balance or those centers associated with respiration, and thus pulmonary oxygenation, are most probably responsible. Other sources of respiratory anoxia, such as pulmonary lesions, obviously must be eliminated clinically. The possibility of stimulation of an erythropoietic center in the mesodiencephalon cannot, however, be completely eliminated.

Summary

Of 106 patients with infratentorial vascular tumors seen at the Mayo Clinic, 38 (36%) had hemoglobin values greater than 15 gm. per 100 ml. of blood. Eleven of these patients had hemoglobin values greater than 18 gm.; papilledema was present in 10 of these 11 patients. Both cystic and solid tumors were found.

In patients with increased hemoglobin and papilledema, the possibility of a vascular tumor in the posterior fossa must be excluded before the papilledema is attributed to the polycythemia alone.

The incidence of absolute polycythemia secondary to cerebellar vascular tumors must be relatively rare. Four patients in this study had blood volume determinations: one had absolute secondary polycythemia, one had a borderline absolute secondary polycythemia, and two had relative polycythemia. The necessity of studies of blood volume in the accurate documentation of these cases is stressed, since these tumors are an adequate cause of relative polycythemia.

Summario in Interlingua

In un gruppo de 106 patientes con tumores vascular infratentorial, vidite al Clinica Mayo, 38 (36%) habeva valores pro hemoglobina de plus que 15 g per 100 ml de sanguine. Dece-un del 38 habeva valores pro hemoglobina de plus que 18 g per 100 ml de sanguine. Papilledema esseva presente in 10 de iste 11 patientes. Tanto tumores cystic como etiam tumores solide esseva trovate.

In patientes qui exhibi nivellos elevate de hemoglobina in le presentia de papilledema il es necessari excluder le possibilitate de un tumor vascular in le fossa posterior ante que le papilledema pote esser attribuite al polycythemia sol.

Le incidentia de polycythemia absolute secundari a tumores vascular cerebellar debe esser relativemente basse. In quatro patientes del presente studio, determinationes del volumine de sanguine esseva effectuate. Un de illes habeva polycythemia secundari absolute, un altere habeva polycythemia secundari absolute de character marginal, e duo habeva polycythemia relative. Es signalate le necessitate de includer

studios del volumine de sanguine in le documentation complete de tal casos, proque le tumores hic discutite representa un causa sufficiente de polycythemia relative.

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THE RESULTS OF TREATMENT IN VARIOUS CLINICAL SYNDROMES *†

By William J. Grace, M.D., F.A.C.P., Ruth H. Pinsky, M.A., and Harold G. Wolff, M.D., F.A.C.P., *New York, N. Y.*

An unusual opportunity presented itself to evaluate the results of therapy in a large group of patients with various stress disorders in one of the medical clinics of the New York Hospital. In a group of 1,154 patients, two different methods of appraisal were used in determining the effectiveness of the treatment—that is, the results of therapy were compared with published series in the literature, and small groups of special disease entities were compared with similar matched groups treated by physicians in other departments of the hospital, using a different method of therapy.

Method of Therapy

Patients with various types of stress disorders were treated in a medical clinic by a group of 31 internists over a period of seven years. The majority of the physicians had had no specific training in psychiatry, although all were well trained internists. A full-time staff psychiatrist saw many of the patients in consultation. Conferences were held regularly with the entire group to discuss the difficult problems and the selected cases presented for demonstrations. A full-time social worker worked in close conjunction with the physicians.

The basis of therapy consisted of measures to alleviate stress in the patient's life. In addition to this, the complete armament of internal medicine was utilized where indicated. The average time spent per patient was approximately 16 hours over a period of nine months.

Clinical Material

Eleven hundred fifty-four unselected patients with various types of stress disorders were treated. The age, sex, marital status, religion, duration of symptoms and severity are given in figure 1. The results of therapy were divided into no improvement, symptomatic improvement, and the category including those patients who were able to reorient themselves and their attitudes toward their environment in such a way that the physician felt future

* Received for publication April 12, 1957.

From the Departments of Medicine and Psychiatry, New York Hospital-Cornell Medical Center, New York, N. Y.

† This work was supported in part by a grant from the Commonwealth Fund, and in part by the Medical Research and Development Board, Office of The Surgeon General, Department of the Army, Contract No. DA-49-007-MD-208.

Requests for reprints should be addressed to William J. Grace, M.D., Director of Medicine, St. Vincent's Hospital, New York City, N. Y.

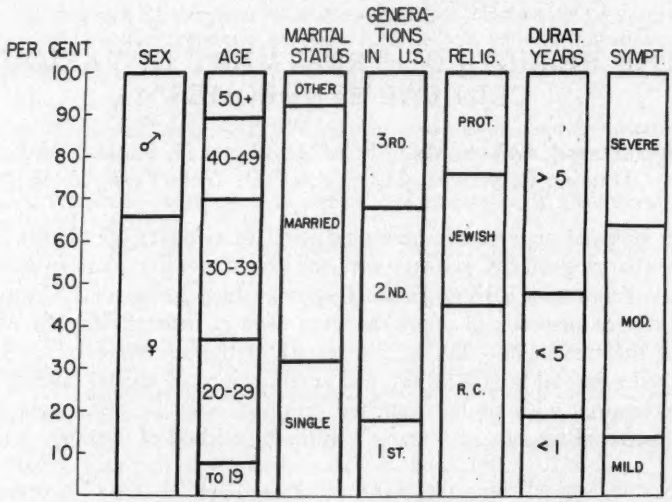

FIG. 1. This figure indicates the data on the 1,154 patients with various stress disorders pertaining to sex, age, marital status, generations of family in the United States, religion, duration of symptoms in years, and severity of symptoms.

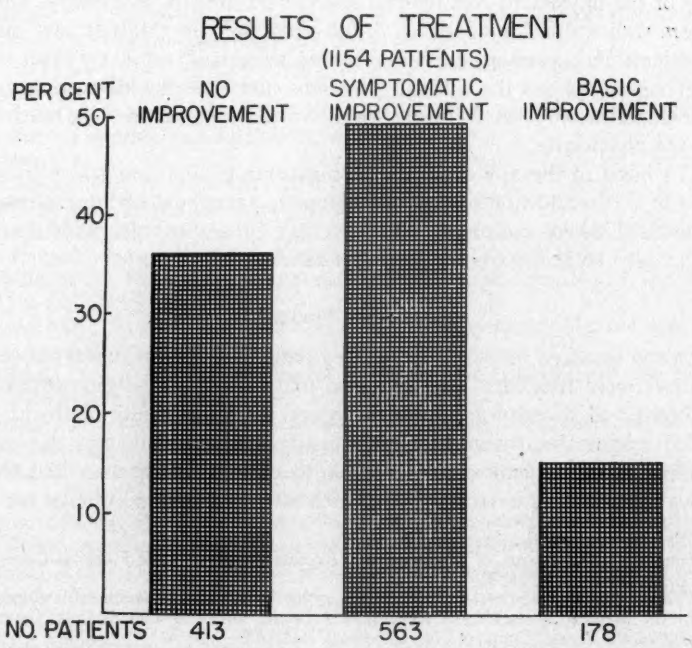

FIG. 2. The results of therapy in the 1,154 patients with various stress disorders are shown, based on an evaluation of the patient by observation and personal interview one year after treatment had been discontinued (see text).

problems could be more adequately handled, and without symptoms. This type of improvement is referred to as basic improvement; patients in this group were, by and large, free of symptoms at the time the evaluations were made.

Results of Therapy

A. *Over-all Clinic Population:* The results of therapy in the entire group of 1,154 patients are indicated in figure 2. It is apparent that approximately one third of the patients are unimproved and that two thirds show improvement. Somewhat less than one fifth of the entire group show basic

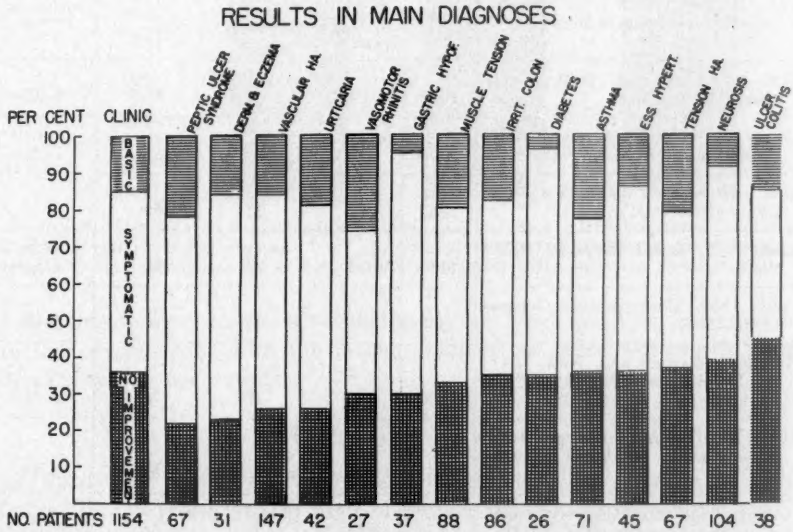

Fig. 3. Results of treatment in the various types of stress disorders according to the diagnostic entities. *Vascular HA* refers to vascular headache, of which migraine is most typical; *Gastric Hypof* refers to patients with gastric hypofunction, as manifested by anorexia, nausea, vomiting, delayed gastric emptying time, and low gastric hydrochloric acid secretion; *Tension HA* refers to patients with muscle contraction (muscle tension) headache; *Neurosis* includes those individuals whose primary diagnosis was psychoneurosis; *Ulcer. Colitis* refers to chronic nonspecific ulcerative colitis. Note that approximately two thirds of the patients are improved, one third unimproved, and about one fifth show "basic improvement" (see text).

improvement and freedom from symptoms. The above estimate is made in the patients evaluated one year after therapy was completed.

Figure 3 shows results of treatment in the main diagnoses. Of the 1,154, 18 required in-patient psychiatric admission.

These results are applicable without significant change in the second and third years following the completion of treatment—that is, at the end of three years, roughly two thirds of the patients continued to maintain improvement over their initial status (figure 4). These results compare favorably with the results of psychoanalytic therapy.[1]

B. *Results in Psychoneurosis:* Of the entire group of 1,154 patients, 104 patients were diagnosed by their physicians as having a primary diagnosis of psychoneurosis. In this group of patients, the results of therapy show that 39% are unimproved, 52% show symptomatic improvement, and 9% basic improvement (figure 3). These results compare favorably with the

TABLE 1

The Results of Psychiatric Therapy for the Psychoneuroses in the Hands of Trained and Skilful Psychiatrists from Various Parts of the World. (Note that roughly two thirds of the patients show improvement.)

Author and Source of Material	No. of Cases	% "Recovered" or "Much improved"	% Improved	Total % Improved	Follow-up Interval (yrs.)
Coon and Raymond, 1940, Stockbridge (1910–1934)	1060	29.9	27.6	57.5	1–20
Carmichael and Masserman, 1939. U. of Chicago Clinics (1935–1937)	66	35	20	55	1–2
Luff and Garrod, 1935, Tavistock Clinic (1928–1931)	355	31	28	59	3
Ross, 1936, Cassel Hospital (1921–1933)	1186	45	25	70	1
Cobb, 1950, Massachusetts General (1933–1948)	200	31	45	76	1–10
Hamilton, Varney and Wall, 1942; and Hamilton and Wall, 1942, New York Hospital (1927–1937)	200	59	17	76	4–15
Miles, Barabee, and Finesinger, 1951, Massachusetts General (1935–1947)	62	23	35	58	2–12
Knight, 1941, Reports of various psychoanalytic sources (1920–1937)	534	45	21	66	—
Fenichel, 1934, Berlin Psychoanalytic Institute (1920–1930)	312	40	18	58	—
Bond and Braceland, 1937, Pennsylvania Hospital (1927–1928)	37	57	19	76	5
Hinsie and Landis, 1937, N. Y. Psychiatric Institute (1930–1935)	119	40	47	87	—
Average percentage with improvement.....				67	

* From Appel, Lhamon, Myers and Harvey.

results of treatment published by various authors who are, in the main, trained and skilled psychiatrists (table 1) [2] or psychoanalysts (table 2).[1] Of these 104 patients, nine had to have in-patient psychiatric admission.

C. *Results of Therapy in Specific Disease Entities:* Certain special disease entities, namely, ulcerative colitis, peptic ulcer and asthma, were evalu-

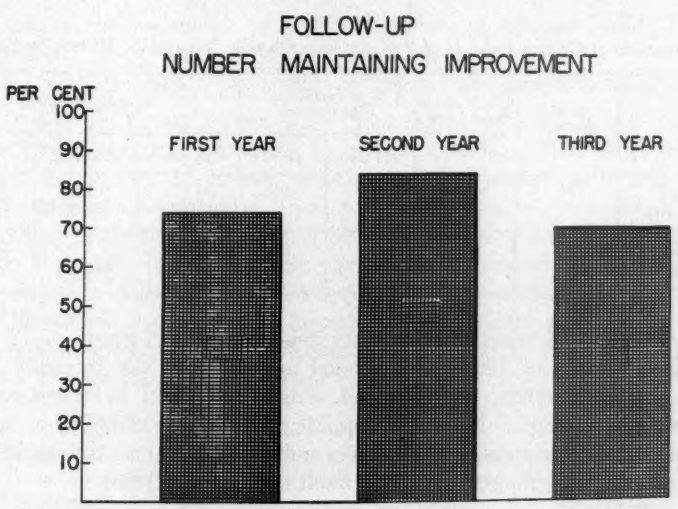

FIG. 4. The number of patients maintaining good results one, two and three years after treatment had been discontinued. Note that the percentage of patients improved remains essentially unchanged, indicating that patients maintained their improved state.

ated by comparing the results of therapy in the hands of physicians working in this special clinic with the results obtained by those working in other departments in the hospital.

ULCERATIVE COLITIS

Thirty-four patients with chronic ulcerative colitis (Group I) were treated by one physician, the basis of therapy being methods designed to alleviate stress in the patient's life. These 34 patients were compared with 34 other patients (Group II) for whom the main emphasis of therapy had been placed on diet, medication and antibiotic agents. The patients in Groups I and II were "matched," patient for patient, with regard to age, sex, severity of illness, duration of illness prior to therapy, age at onset, and x-ray changes. There were 24 women in each group. The patients ranged in

TABLE 2

Results of Therapy of Psychoneurosis by the Formal Psychoanalytic Method. (Note that roughly two thirds of the patients are improved.)

Source of Material	No. of Patients	Improved
Berlin Institute Report	274	62%
Hyman and Kassel	33	49%
London Clinic Report	74	50%
Chicago Institute	157	62% of the psychoneurotic pts. 50% of the sexual disorders.
Menninger	31	80%

* From Knight, Am. J. Psych. 98: 434, 1941.

TABLE 3

Comparison of Groups I and II of Patients with Chronic Nonspecific Ulcerative Colitis

	% of Women Patients	% of Patients Aged 15–34 at Onset of Illness	% of Patients in Age Groups		Severity of Illness		
			15–34	25–34	Severe	Moderate	Mild
Group I (34 Pts.)	71	88	70	11	20 Pts. (60%)	9 Pts. (26%)	5 Pts. (14%)
Group II (34 Pts.)	71	88	70	11	20 Pts. (60%)	9 Pts. (26%)	5 Pts. (14%)

age from 15 to 54 years, the majority being in the age group of 15 to 34. The severity of the illness was graded according to the intensity of the symptoms of diarrhea, bleeding and weight loss, and by the x-ray and proctoscopic findings. In each group, 20 (60%) were classified as severely ill, nine (26%) as moderately severe, and five (14%) as mildly ill. The duration of illness ranged from one month to over 10 years.

TABLE 4

Duration of Illness, Groups I and II

Less than 1 month	2 Patients
1 to 6 Months	4 Patients
6 to 12 Months	6 Patients
1 Year to 2 years	7 Patients
2 Years to 5 years	6 Patients
5 Years to 10 Years	6 Patients
10 Years or more	3 Patients

In Group I all of the patients were managed by one physician (W.J.G.), the emphasis on therapy being directed mainly at alleviating stress in the life of the patient. Those in Group II were seen by a group of four physicians. The main emphasis on therapy in the patients in Group II was on diet, and antispasmodic and chemotherapeutic agents. In Group II the patient did not always see the same physician on each visit. Although the therapeutic effectiveness of frequent visits to a physician must be considered in Group II, the major emphasis in this group was not placed on attempting

TABLE 5

Results of Therapy in Patients with Chronic Nonspecific Ulcerative Colitis. The difference between Groups I and II in terms of deaths, operations and complications is statistically significant at the 5% level of confidence.

	Deaths	Operations Ileostomy and Colectomy	Complications	Worse Including Operations and Death	No Change	Improved	Symptom Free
Group I 34 Patients	3 Patients (8.8%)	1 Patient (2.9%)	6 Patients (17.7%)	4 Patients (11.8%)	8 Patients (23.5%)	13 Patients (38.2%)	9 Patients (26.5%)
Group II 34 Patients	6 Patients (17.6%)	10 Patients (29.4%)	20 Patients (58.8%)	16 Patients (47.0%)	7 Patients (20.6%)	6 Patients (17.6%)	5 Patients (14.7%)

deliberately to relieve stress. All of the patients in Groups I and II have been observed for at least two years (tables 3 and 4).

Results of Treatment: The results of therapy are shown in table 5.

1. *Deaths:* In Group I there were three deaths (8.8%). Two patients died following surgical operations in other institutions; the other patient died in a distant city 10 months after leaving the writer's care and while under the care of a psychiatrist.

In Group II six patients died. Two of these were postoperative deaths; the other four were due to multiple venous thromboses and pulmonary emboli, perforation of the sigmoid, paralytic ileus, and infarction of the lungs.

2. *Operations Performed:* In Group I three patients were subjected to ileostomy and, subsequently, to colectomy. In Group II 10 patients had an ileostomy and/or colectomy at a later date.

TABLE 6

Comparison of Incidence of Serious Complications in the Two Groups of Patients with Chronic Nonspecific Ulcerative Colitis

	Group I (34 Pts.)	Group II (34 Pts.)
Patients with complications	6 (17.7%)	20 (58.8%)
Arthritis	1	5
Thrombophlebitis	1	4
Erythema nodosum	0	3
Fistula fissure	1	3
Abscess	1	
Polypoid degeneration	1	7
Stricture	1	1
Hemorrhage	2	1
Embolism	1	2
Perforation	1	1
Cancer	0	0

3. *Results of Treatment in Terms of Symptoms:* When those patients who died or who were subjected to operation are excluded, none of the patients in Group I became worse, whereas in Group II two patients became worse. If operations and deaths are to be included, then four patients became worse in Group I, 16 in Group II.

Twenty-two patients, or 65% of Group I, were improved (nine, or 26% of these having been symptom-free for two years or more). Eleven patients, or 32% of Group II were improved (five, or 14.7% being symptom-free).

4. *Complications:* There were serious complications in six patients in Group I, as compared with 20 in Group II. Of the serious complications, perforations of the bowel occurred in one patient each in Groups I and II. Serious hemorrhage occurred in two patients in Group I and in one patient in Group II; severe arthritis occurred in one patient in Group I and in five patients in Group II (table 6).

5. *Time Spent in Hospital:* The average number of patient-hospital-weeks per year in Group I was nine and one-half, and in Group II, 11.5

TABLE 7

Comparison of Patients with Chronic Nonspecific Ulcerative Colitis in Terms of Changes in X-Rays Over a Minimum of Two Years of Observation

	Improved	No Change	Worse
Group I	4	16	4
Group II	1	9	17

weeks. Fifty-three per cent of the patients in Group I were never hospitalized, as compared with 29% of those in Group II who were not hospitalized.

6. *Number of Visits to Physician:* The number of visits made by the patient to the out-patient department per year is approximately the same in Groups I and II: 24 visits per patient per year in Group I as compared with 21 visits per patient per year in Group II.

7. *Changes in X-rays:* Changes in x-rays are shown in table 7. In Group I, four patients showed considerable improvement in the x-ray appearance of their large intestine during the course of two years of therapy, as compared with only one patient showing improvement in Group II. Four patients in Group I showed progressive changes in the x-ray, as compared with the 17 patients in Group II showing such changes.

The differences between Groups I and II are statistically significant.

PEPTIC ULCER AND ASTHMA

Similarly, a group of 23 patients with peptic ulcer and 27 patients with asthma were compared with matched cases taken from other departments of the hospital (tables 8 and 9, figure 5). In these groups (peptic ulcer and asthma) it is apparent that the results of treatment by those who con-

TABLE 8

Results of Treatment in Two Groups of Patients with Duodenal Ulcer. (The two deaths in Group I occurred following gastric surgery performed at other hospitals after the patients had left treatment in the New York Hospital.)

Clinical

	Died	Operation	Worse	Same	Improved
Group I (23 Pts.)	2	5 (inc. 2 deaths)	0	4	14
Group II (23 Pts.)	0	9	1	7	6

X-Ray Changes

	Worse	Same	Improved	No Information
Group I (23 Pts.)	5	6	9	3
Group II (23 Pts.)	10	2	11	0

TABLE 9
Peptic Ulcer Complications

	No. of Patients Having Complications	Hemorrhage	Obstruction	Perforation
Group I (23)	6	5	3	0
Group II (23)	10	7	5	1

cerned themselves with stress in the patient's life were often at least twice as good as in the hands of physicians who did not.

Comparison of Results of the Treatment of Peptic Ulcer with the Results of Psychoanalytic Treatment of Patients with Peptic Ulcer: The group of patients with peptic ulcer mentioned above was also compared with those patients with peptic ulcer who had repeated intensive psychoanalytic therapy.[8] The results of psychoanalytic therapy are given in table 10. Although the number of patients is small in this group, it is apparent that the results of therapy are no better than are the results achieved by those who used a technic not psychoanalytic.

OUTLINE OF MANAGEMENT

Treatment was carried out in interviews spaced at intervals of a few days or weeks, according to the apparent needs of the subject. In the

TABLE 10
Results of Treatment in Patients with Duodenal Ulcer by Psychoanalytic Therapy. (Note that results of therapy by this technic are no better than are results of treatment of duodenal ulcer reported by others using methods based upon diet and medication. Two of seven patients (roughly one third) are unimproved.)

Case No.	Ulcer Activity			Follow-up Period	Ulcer Improvement	Personality Improvement
	Before	During Analysis	After			
II	+ 3 yrs. before	0	++ 6 mos. after	2 years	0	++
X	++	Decreasing to 0	0	1½ years	++	++
XI	++	++	+	5 years	+	++
XII	++	+	0	1¼ years	++	++
XV	++ 4 yrs. before	0	++ 6 yrs. after	8 years	0	++
XVI	++	++	+	2 years	+	+
XVII	++	++	+	½ year	+	++

* From Stine and Ivy.

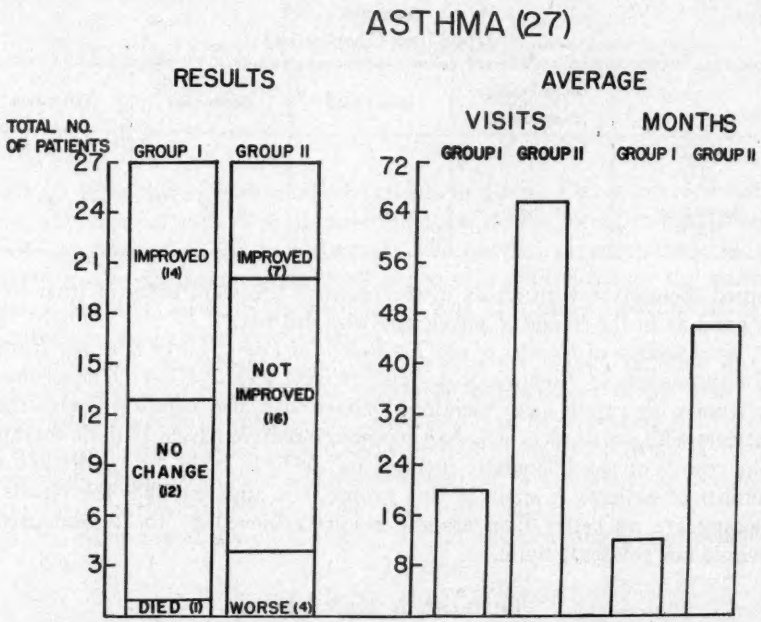

FIG. 5. Results of treatment in two groups of patients with bronchial asthma. Note that in Group I more patients are improved, and that less time was spent with the patients, than in Group II, where the basis of treatment was medication and desensitization procedures.

interview the physician's role was that of a detached but interested, reliable, consistent and supporting confidant. In the interviews the patient was encouraged to express himself freely, to engage in introspection, to recall, relate and interpret dreams, and to make associations with his thoughts, feelings and life events. Therapy was directed toward bringing about an understanding of himself, and encouraging him to make a more constructive orientation toward his life and the people in it.

The greatest benefit to the patient was a good physician-patient relationship. The patient was given opportunity and encouragement to express—with a free show of feelings, to a sympathetic and appreciative physician—the major complaints and difficulties in his life situation. The physician never criticized such feelings. He encouraged the patient to express his thoughts, and to be confident that such attitudes would not threaten his relationship with others, or exclude him from the love of his closest relatives. Ambivalent feelings toward a spouse or parent were discussed, and the universality of such attitudes was explained.

Encouragement and support of the patient were freely given by the physician. These employed the warmth of human relationships. The patient's own assets and accomplishments were emphasized in building the

self-esteem and self-confidence of the patient. A tolerant attitude on the part of the physician was essential. No problem could be too small to consider; interviews with spouses and relatives were often necessary. Special consideration was given the patient during periods of unusual stress. He was told he could telephone the physician at almost any time, and was permitted to make earlier appointments when difficult situations arose. During times of severe symptoms the patient was seen frequently—as often as daily—if such care was required.

Patients were given an explanation of the disease process, and this was repeated frequently, especially during periods of severe symptoms. Emphasis was placed on the participation of the bodily viscera in different moods and feeling states. Periods of illness were correlated with periods of emotional stress.

In addition to the usual "routine" medical history, a detailed personal biography was undertaken. The greatest emphasis was placed on the reaction of the patient to the immediate environment at the time of the appearance of the symptom. An attempt was made to understand each exacerbation of symptoms in terms of a complete description of the precipitating situation, as well as a detailed description of the reaction of the patient to it. In this way periods of illness were correlated with periods of emotional stress. The background, the family, the cultural setting, the emotional responses, and the aims and ambitions of the patient were explored in order to understand the patient and to help him to understand himself. In some instances it was possible for the patients to recognize the basis of their feelings and attitudes from previous experiences, and to alter them significantly, and for the better. However, many patients were unable to incorporate this knowledge into their daily behavior, and symptoms did not change. In such instances it was felt better to have the patient realize and accept his dependent position and to make the best of it, rather than to try to alter it. That the need to be cared for and loved is universal and acceptable was emphasized, as was the fact that attempts to reject the dependency are often more disastrous than is the acceptance of a dependency.

The patients were instructed in means of recognizing their own manifestations of accumulating emotional tension, and encouraged (1) to accept them for what they represented, and (2) to attempt to deal with the circumstances leading to their presence. When the patients learned to recognize the origin of their symptoms, they often no longer looked on them as the manifestations of a dire disease. This awareness in itself helped to alleviate anxiety.

Finally, rearrangement in the environment was attempted. When successful, it usually produced dramatic results in terms of symptomatic relief. Unfortunately, however, this was not always feasible, because of the lack of a practical maneuver, the lack of coöperation of the family, or the inability of the patient to accept any drastic change.

The situation was worked out with the patient. The patient's ability to utilize his own resources determined the final result. The physician guided him, helped him understand why he was getting into difficulty, and supported him when he was trying to alter his environment or attitudes.

The passage of time, in itself, was often helpful in establishing the patient's confidence in his physician. The increase in confidence frequently alleviated inhibitions and reluctance to express feelings and attitudes. Moreover, an appreciation of the appropriate moment for introducing a new concept or challenging an established attitude was essential. Thus it would have been unwise when the patient was disturbed or having severe symptoms to threaten his security system in any way. Difficulties in the life situation were often anticipated so that interviews might be arranged to antedate an approaching unpleasant event, such as school examinations, the undertaking of a new position, or the approaching visit of an unwanted relative.

Time factors were of the greatest importance in this type of management. In many instances, in hospital circumstances, an apparently spontaneous recovery took place in two or three months, representing the therapeutic effect of the passage of time and of autonomous biologic forces.

Discussion

In the over-all clinic population and in the group of patients diagnosed as having psychoneurosis, the results of therapy by internists who place special emphasis on alleviating stress in the patient's life compare favorably with reports from other clinics where the treatment is carried out by trained psychiatrists. The data indicate that, in the hands of a sympathetic, sincere, informed and well trained physician, approximately two thirds of the patients will recover or show considerable improvement, and one third will show no improvement. Other authors have similarly indicated the effectiveness of therapy of stress disorders by internists. For example, in neurocirculatory asthenia,[4] a series of patients receiving formal psychotherapy did no better than did those managed by internists (table 11).

It is of importance to be able to compare these studies with reports in which the patients received no treatment. Unfortunately no such data are available. In a group of 237 psychoneurotic patients reported by Fries and Nelson, only 40% showed improvement when little or no "psychotherapy" was attempted in a general medical clinic.[5]

In certain disease entities—namely, peptic ulcer, ulcerative colitis and asthma—results of therapy by those who made protracted efforts to alleviate stress in the patient's life were better than they were in the hands of those who did not; as to peptic ulcer, the results were better than they were with those using psychoanalytic therapy. In addition, with these patients, frequently less time was required to be spent with the patient than when the physician concerned himself almost entirely with diet and medication. In the initial months of this type of treatment, more time is spent with the

patient than in the more usual therapy. However, over a period of a year less time is often spent.

It is possible that the one third of the patients showing no improvement represent the group of patients for whom there is no effective therapy at the present time. The findings show that internists, psychiatrists and psychoanalysts are all effective to the same extent in the treatment of psychoneurosis. This suggests that the common denominator is a sincere, sympathetic physician and a good doctor-patient relationship, rather than the special technic used by the therapist. This theory is enforced by the observation of Miles et al.,[6] in a study of 62 patients, that the psychiatric residents and interns were as effective in therapy as were the more senior and experienced psychiatrists.

TABLE 11

Results of Treatment of Patients with Neurocirculatory Asthenia in the Hands of Internists (Wheeler et al.), Compared with Various Types of Psychiatric Therapies. (Note that in all groups approximately two thirds are improved and one third unimproved.)

Status	Wheeler, White, Reed, Cohen, 60 Cases, Per Cent	Sanatorium Plus Psychotherapy 1–20 Yr. Follow-up of 678 Cases, Per Cent	Psychoanalysis of 24 Cases, Per Cent*	Outpatient Psychotherapy	
				3 Year Follow-up of 214 Cases, Per Cent	End of Treatment of 24 Cases, Per Cent
Well	11.7	8.3	16.7	34.6	12.5
Symptoms, no disability, much improved	35.0	38.5	54.2	31.3	29.2
Symptoms, mild disability, slightly improved	38.3	43.2	16.7	5.1	25.0
Symptoms, moderate or severe, disability, no change, worse	15.0	10.0	12.4	29.0	33.3

* Seven patients who failed to complete at least six months of analysis and who were termed "therapeutic failures" are omitted.

It is apparent from these data that internists can do a very effective job in helping the patients to alleviate stress in their lives, with its associated relief of symptoms. It is suggested that the internist attempt to assume more responsibility for his patients in terms of alleviating stress, and that he use the psychiatrist as an expert and consultant for those patients he is not able to help, rather than refer all patients with stress disorders to the psychiatrist.

CONCLUSIONS

Patients under the care of internists, with main emphasis of therapy on diet, medication and antibiotic agents, did less well than did those under the care of a single well trained internist who devoted much attention to alleviа-

tion of stress in the patient's life. His results were, in turn, about as satisfactory as those attained by psychiatrists and psychoanalysts in other clinics.

Summario in Interlingua

Un population de 1.154 patientes von varie typos de disordine somatic associate con experientias stressante in lor vita esseva tractate per 22 medicos in un clinica special. Le base del therapia in omne iste casos esseva le effortio de alleviar le stress in le vita del patientes. In plus, le usual mesuras medicinal e dietari esseva usate ubicunque illos pareva appropriate. Le medicos esseva internistas, e solmente paucos inter illes habeva habite un formal preparation psychiatric.

Le resultatos de iste genere de therapia esseva analysate secundo le procentages de patientes meliorate, non-meliorate, e pejorate a periodos de un a cinque annos post le initiation del tractamento. Le datos colligite concerne 104 patientes con le diagnose de psychoneurosis e 1.050 patientes con varie syndromes clinic in que le stress del vita ha cognoscitemente un rolo importante, i.e. per exemplo urticaria, mal de capite, hypertension, ulceres peptic, e colitis ulcerative. Le resultatos del therapia pro psychoneurosis es comparate con un collection de datos ab publicate series de patientes psychoneurotic tractate per le usual technicas psychiatric inter le manos de psychiatros experte, frequentemente in hospitales psychiatric. Le datos indica que circa duo tertios del patientes esseva meliorate in le presente serie e le mesme proportion in le series reportate in le litteratura.

In le caso del patientes con asthma, hypertension, ulcere peptic, colitis ulcerative, e eczema, le resultatos obtenite in le presente serie es comparate con appareate series de patientes con simile disordines tractate secundo le methodos conventional in que mesuras dietari e/o medicinal es le base del therapia. Le patientes esseva appareate secundo etate, sexo, duration e severitate del morbo, e alterationes radiographic. Le resultatos therapeutic obtenite in patientes qui esseva tractate per medicos accostumate a sublinear le factor del stress in le vita de lor malados esseva a minus duo vices melior, e le tempore requirite per le tractamento esseva plus breve. Finalmente, in le caso de asthma, eczema, e ulcere peptic, le resultatos therapeutic obtenite a iste clinica es comparate con le resultatos obtenite in publicate series in que un therapia psychoanalytic esseva usate. Le resultatos del tractamento psychoanalytic es minus bon que le resultatos obtenite in iste clinica.

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A CRITICAL REVIEW OF CIRCULATORY PHYSIOLOGY AS IT APPLIES TO CEREBRAL VASCULAR DISEASE*

By PERITZ SCHEINBERG, M.D., *Miami, Florida*

THE importance of vascular disease of the brain in clinical medicine has recently received renewed emphasis in the medical literature by virtue of increasing awareness of the high statistical incidence of this problem and the mortality and morbidity which it produces.[1] In addition, considerable encouragement concerning possible effective therapy has resulted from observations indicating that anticoagulants may be of value in preventing the occurrence or recurrence of certain types of cerebral vascular lesions.[2, 3, 4] These factors have stimulated a reëvaluation of the clinical course of the various types of cerebral vascular diseases in the hope that a more thorough knowledge of the natural histories of these conditions may shed additional light on their pathogenesis and, eventually, on their treatment. Further attacks on this problem have emanated from the laboratories of the various medical and neurologic specialties, with the resultant accumulation of data pertaining to the gross and microscopic anatomy of the cerebral vessels, the pathology of cerebral vascular disease, the chemistry of brain tissue in normal and pathologic states, and the physiology of the cerebral circulation.

The critical reader does not have to be reminded that it is not always possible to transpose physiologic data obtained in a laboratory directly to the bedside of the sick patient. As will be pointed out in this review, clinical application of such data does not necessarily result in a successful therapeutic method. Much of the information pertaining to cerebral circulation and metabolism has been obtained by means of the nitrous oxide technic for measuring cerebral blood flow, and the subjects may have been healthy individuals in whom the physiologic effect of a certain drug or mechanical maneuver was determined. It is risky to explain the clinical phenomena of cerebral vascular disease from data obtained in this way. Further, it needs to be reëmphasized that the nitrous oxide technic does not adequately measure local blood flow or metabolic changes in the brain. Despite these limitations, much useful information has accumulated, and it is the purpose of this review to summarize the circulatory physiologic studies which have been done on patients of many types with the idea of relating these physiologic data to the clinical and pathologic problems of cerebral infarction due to thrombosis or embolism, hypertensive cerebral hemorrhage, and hyperten-

* Received for publication September 23, 1957.

From the Department of Medicine, Division of Neurology, University of Miami School of Medicine, Jackson Memorial Hospital, Miami, Florida.

Requests for reprints should be addressed to Peritz Scheinberg, M.D., Associate Professor of Neurology, Jackson Memorial Hospital, Miami 36, Florida.

sive encephalopathy. It is surprising to note how frequently one cannot explain clinical phenomena by physiologic data; indeed these obvious discrepancies may do no more than delineate areas where more detailed clinical and physiologic observations are necessary.

With these precautions in mind it is possible to proceed to a discussion of the various factors known to influence cerebral blood flow, cerebral metabolism and cerebral vascular resistance, and how these factors may relate to some of the problems of cerebral vascular disease.

I. *Effective Arterial Pressure:* There is little doubt that this is one of the most important of the variables influencing the rate of cerebral circulation, and clinically it also appears to have a significant role in the pathogenesis of cerebral vascular thrombosis and in the occurrence of transient cerebral ischemia without evident infarction.[5] Clinicians are aware that transient, and occasionally permanent, neurologic symptoms may appear in patients, particularly in the middle and old age groups, with acute systemic hypotension. This may occur immediately following myocardial infarction, acute blood loss, simple faint, traumatic shock, severe postural hypotension (as in hyponatremia or diabetic neuropathy), or the Stokes-Adams syndrome.

There is no evidence to indicate that cerebral blood flow slavishly alters with changes in arterial pressure, but there is no doubt that changes in cerebral blood flow do occur as a result of arterial pressure changes. Direct observations of the pial vessels of the cat through a Forbes window have shown that a fall in arterial pressure is a strong stimulus for the production of pial vasodilatation,[6] although no direct observations on deeper cerebral vessels have been made. Postural alterations in humans have indicated that cerebral blood flow is unaltered in a 20° head-up tilt,[7] but that tilting normal young subjects to the erect posture with subsequent 34% fall in effective cerebral arterial pressure resulted in 21% decrease in cerebral blood flow and a 16% decrease in cerebral vascular resistance.[8] It is thus evident that a sufficient reduction in arterial pressure may result in diminished cerebral circulation in the normal subject, even though the cerebral vessels may dilate in response to the decreased pressure. The above studies also indicated that, as cerebral blood flow is decreased, a compensatory mechanism in the form of increased oxygen and glucose extraction from the blood maintains normal cerebral metabolism. Eventually, however, this compensatory mechanism breaks down and cerebral metabolism decreases. In the studies mentioned, fainting frequently occurred at this point.

Relatively few studies are available on the effects of acute hypotension in subjects usually normotensive. Observations on blood flow in the cat or rabbit brain indicated that rate of circulation remained normal as long as the arterial pressure was above 30 mm. of Hg, but a rapid decline of cerebral blood flow, usually followed by death, occurred below this level.[9] The observations of Fazekas, Kleh and Parrish in 11 patients in shock due to a

variety of causes indicated that there was a striking reduction in cerebral blood flow from normal, and that cerebral metabolism was also reduced below normal. The findings varied from patient to patient, suggesting that during shock compensatory mechanisms help to maintain cerebral metabolism despite the reduction of arterial pressure and cerebral blood flow, but that eventually these mechanisms fail.

The majority of studies on the effects of induced hypotension on cerebral circulation and metabolism were performed in patients with hypertensive vascular disease. All of these studies indicate that no matter what agents are used to lower arterial pressure, cerebral blood flow remains normal by virtue of cerebral vasodilatation, so long as the blood pressure does not fall below normotensive values. If this occurs, cerebral blood flow is usually reduced, and further drop in blood pressure was followed by a diminution of cerebral metabolism, and, frequently, alterations in the patient's alertness or consciousness.[11, 12, 13, 14, 15, 16, 17] It is of value to note that in one of these studies,[17] signs of cerebral anoxia were noted clinically in some of the patients despite the absence of a statistically significant drop in cerebral blood flow or metabolism. The authors suggested that the vasodilatation produced in patients with atherosclerosis may occur chiefly in less diseased vessels, and at the expense of a further impairment of circulation through the more severely involved vessels.

These observations on the cerebral circulation therefore seem to confirm the clinical impression that acute hypotension may play a role in the pathogenesis of some types of cerebral vascular accidents. As blood pressure falls, compensatory cerebral vasodilatation occurs, but eventually a point is reached, particularly in the subject with atherosclerosis and arteriosclerosis of cerebral vessels, at which the arterial pressure head is no longer sufficient to supply the metabolic needs of the brain, and symptoms ensue. It might seem logical to extend such reasoning to the conclusion that this cerebral ischemia may result in infarction, but physiologic proof of this is as yet lacking in humans. Studies in animals have shown that in circumstances in which neither local restriction of cerebral blood flow (by reducing the caliber of a major artery) nor hypotension alone is sufficient to cause brain ischemia or infarction, localized cerebral encephalopathy occurs when both occur together.[18] In two subjects with recurrent ischemic attacks from what was thought to be impending internal carotid artery occlusion, reduction of effective cerebral arterial pressure by tilting to the upright position did not induce the symptoms of focal cerebral ischemia, even though generalized electroencephalographic abnormalities appeared.[19] It is thus evident that the role of hypotension in the etiology of cerebral infarction due to thrombosis of atherosclerotic vessels or in the syndrome of recurrent ischemic attacks is not yet clear and merits further study.

At the other end of the clinical spectrum pertaining to effective arterial pressure and its role in the regulation of cerebral circulation is hypertension.

The etiology of cerebral hemorrhage in the great majority of cases is thought to be in some way related to hypertension. At the present time no theory which has been projected in explanation of this relationship is considered to be adequate. Pathologic studies have not clarified this problem, and there are many who take issue with Globus' concept of hemorrhage into an area of ischemic infarction as the true pathogenesis.[20] The relationship between hypertension and cerebral vascular thrombosis with infarction is presently thought to be due to the increased atherosclerosis and arteriosclerosis which accompany hypertension.

The effects of hypertension on cerebral circulation have been studied many times. These observations have all shown that cerebral blood flow and metabolism are normal in hypertensive patients who do not have associated severe atherosclerosis.[21, 22, 23, 11, 12, 13, 14, 15, 16] The normal blood flow is apparently due to a striking increase in cerebral vascular resistance, which is indicative of a constriction of cerebral vessels in hypertension. This increased tonus in the cerebral vessels can be relaxed by reducing the blood pressure by means of differential spinal anesthesia, sympathectomy, or injections of dihydroergocornine, hexamethonium, phenoxybenzamine, hydergine or Veriloid, with the result that cerebral blood flow is still maintained at normal levels provided arterial pressures are kept at the normotensive range.[11, 12, 13, 14, 15, 16, 17] Even in hypertensive encephalopathy, with neurologic changes as a part of the clinical picture, cerebral blood flow and metabolism were normal.[16]

The available physiologic data do not offer a satisfactory explanation of the relationship of hypertension to brain hemorrhage or to cerebral thrombosis with infarction, unless there is some significance in this regard, as yet not understood, to the intense cerebral vasoconstriction which occurs in hypertension. It is conceivable that this increased vascular tone may eventually cause some injury to the arterioles which might be the initiating factor in hypertensive cerebral hemorrhage. Such a concept is entirely speculative but is worthy of further investigation.

II. *Cerebral Vascular Resistance:* Reference has already been made to the importance of the tone of cerebral vessels in the regulation of cerebral blood flow in hypertension and in induced hypotensive states. Cerebral vascular resistance can be defined as the composite of all the factors which tend to hinder blood flow through the brain. In physiologic studies, it is measured as the quotient of the difference between mean arterial pressure and cerebral venous pressure divided by cerebral blood flow. This measures not only the tone of cerebral vessels but also the effect of organic changes of the vessels, the influence of nervous innervation of the cerebral vessels, the viscosity of the blood, the intracranial pressure, the effects of chemical substances in the blood on the cerebral vessels, and the local brain tissue requirements.

1. *Aging, Cerebral Arteriosclerosis, and Other Organic Changes in Cerebral Vessels.* The increased incidence of brain infarction due to vessel

thrombosis in elderly individuals and those with cerebral arteriosclerosis is well established clinically. It has been assumed that this is due to the increased tendency for thrombi to occur in vessels whose lumina have been reduced by atherosclerotic or arteriosclerotic change, with resultant restriction of cerebral blood flow. The laboratory observations pertaining to this problem appear to substantiate this clinical concept, although there is yet no satisfactory explanation for the predilection of certain vessels and certain areas of the brain to be involved much more frequently than others.

There is fairly general agreement that aging results in a decrease in cerebral blood flow and an increased cerebral vascular resistance.[24, 25, 26, 27] One study revealed no reduction in cerebral blood flow due to aging per se [28] though clinical distinction between a "normal" old person and one who has cerebral vascular disease without neurologic complications would be most difficult. Except for the first decade of life, during which cerebral blood flow and cerebral oxygen consumption are high and cerebral vascular resistance is low as compared to normal young adults,[28] cerebral metabolism as specifically and incompletely reflected in cerebral oxygen and glucose consumption seems to remain fairly stable until after middle age (above 55 to 60 years of age), when it decreases with advancing years. This is undoubtedly another example of the ability of the brain to compensate for diminishing cerebral blood flow by extracting increasing quantities of oxygen and glucose from the blood. It is not clear why this compensatory mechanism fails so early in the aging brain, since oxygen and glucose extraction are increased only slightly, and not nearly to the anticipated capacity that the cerebral circulation demonstrates in other situations, such as motionless standing [8] or congestive heart failure.[29]

There are several alternative explanations for the changes observed in aging. One of the studies indicated that cerebral vascular resistance increased prior to any change in cerebral metabolism.[25] If this is actually the case, it is evident that the increased resistance of the vessels is the primary factor and is responsible for reduction of cerebral blood flow, as indicated above. The eventual reduction of cerebral metabolism might be due to (1) progressive dysfunction of brain cells due to ischemia induced by narrowed cerebral vessels; (2) gradual and natural reduction in the number of functioning and metabolizing brain cells; (3) decreased metabolic needs of the individual cells with aging, perhaps due to decreased cellular enzyme activity. Definitive proof is lacking for any of these possibilities or for any of several others which might conceivably be invoked, but the available evidence points most strongly to the belief that the reduction of cerebral metabolism in the aged is due to ischemia resulting from the increased resistance offered by atherosclerotic and arteriosclerotic cerebral vessels.

Physiologic studies directed toward determining the effect of cerebral arteriosclerosis on cerebral circulation have been confused by the frequent coexistence of old age and hypertension. There is general agreement that patients with known cerebral vascular disease show a reduction in cerebral

blood flow and increased cerebral vascular resistance, but to what extent is not yet clear. There is no definite evidence to indicate that patients with clinical cerebral vascular disease, with or without current neurologic changes, show alterations in cerebral circulatory and metabolic functions beyond that seen in patients of similar age without evident vascular disease of the brain.[23, 25, 27] The data do reveal that if cerebral vascular disease is accompanied by alterations in mental status there is a significant reduction in cerebral blood flow and cerebral oxygen and glucose utilization, and an increase in vascular resistance,[30] but this may be nothing more than testimony to the degree of severity of the vascular disease in these patients. There are discrepancies in the published data for which there is no explanation. Scheinberg found that in patients with hypertension and cerebral vascular disease with no alteration in mental status, normal values (for that age group) for blood flow and oxygen and glucose consumption were observed,[30] whereas Shenkin and colleagues found that the combination of hypertension and atherosclerosis produced significant reductions in blood flow and metabolism.[23] The observations by Freyhan, Woodford and Kety,[31] when compared with hypertensive and arteriosclerotic patients of the same age group, would, according to Shenkin,[23] vitiate their conclusion that the reduced cerebral blood flow and oxygen consumption are responsible for the abnormal mental symptoms their patients displayed, whereas their conclusions would fit quite well with the observations on patients with cerebral vascular disease with accompanying mental status changes reported by Scheinberg.[30]

Physiologic studies in patients with primary thrombosis of the internal carotid artery revealed no circulatory or metabolic abnormalities specifically attributable to the carotid occlusion,[32] but were similar to results obtained in other middle aged patients with cerebral arteriosclerosis. Unilateral internal carotid artery ligation in four patients resulted in a marked increase in cerebral vascular resistance subsequent to surgery. In one patient whose cerebral vascular resistance was elevated prior to surgery, ligation of the carotid resulted in immediate development of hemiplegia, with further rise in cerebral vascular resistance.[33] It has been suggested [32] that increased cerebral vascular resistance is a contraindication to carotid ligation, but this would exclude almost all middle aged patients, and surely all those with hypertension. The occurrence of neurologic complications following acute carotid ligation for congenital aneurysm is well known clinically;[34, 35] the reported increase in cerebral vascular resistance which accompanies this procedure is a logical explanation for the occurrence of this phenomenon in individuals whose cerebral circulation is compromised even prior to surgery.

Available information does not offer an entirely satisfactory explanation for the occasional occurrence of thrombosis of one internal carotid artery without the development of neurologic deficit. It is possible that gradual

development of the thrombosis may permit the development of collateral circulation in time to be useful. The route of this collateral circulation has been demonstrated in three patients to be by way of the external carotid circulation to the eye, and thence by the ophthalmic artery to the intracranial portion of the internal carotid.[36] Such a pathway could be of value only if the thrombosis remains in the cervical portion of the carotid. Variations in the circle of Willis also undoubtedly account for the variability in symptomatology which occurs following carotid thrombosis.

Physiologic studies are lacking in cerebral vascular disease due to causes other than atherosclerosis, except for a series of patients with symptomatic neurosyphilis.[37] These subjects showed slowed cerebral blood flow, diminished cerebral oxygen consumption, and increased cerebral vascular resistance. Although occlusion of cerebral vessels in neurosyphilis is recognized pathologically, this disease is also associated with cortical atrophy not frequently seen in vascular disease of arteriosclerotic origin,[38] so that it is not possible to be certain if the reduction in cerebral blood flow noted in these patients was primary and due to reduction in the lumen of the cerebral vessels, or was secondary to parenchymal disease with disturbance of brain metabolism.

The reactivity of cerebral blood vessels is probably of clinical importance in cerebral vascular disease, since the ability of these vessels to dilate in response to various stimuli seems to be their means of compensating and maintaining a stable cerebral metabolism in the face of diminished arterial pressure or slowed blood flow. Available data indicate that in elderly subjects, and those with cerebral arteriosclerosis, cerebral blood flow is increased much less and cerebral vascular resistance decreased less than in normal young subjects following inhalation of 5% carbon dioxide, normally a powerful cerebral vasodilator.[24, 39] It is of interest to note that patients with hypertension and arteriosclerosis responded normally to carbon dioxide inhalation, with marked reduction in cerebral vascular resistance, which still, however, remained elevated above normal. That portion of the increased vascular resistance due to vasoconstriction can therefore be removed by appropriate vasodilators, but not so that component which is due to narrowing of the lumina of cerebral vessels by atherosclerosis and arteriosclerosis. This lack of responsiveness may imply rigidity of the vessel walls, or might also signify that chronically reduced blood flow and oxygen-deprived tissue have resulted in a constant local dilatation of cerebral vessels so that further dilatation is no longer possible.

Since the nitrous oxide procedure measures blood flow per unit weight of brain tissue, very few conclusions concerning possible alterations in local blood flow in different areas of the brain can be deduced from these studies. Bessman, Alman and Fazekas [17] suggested that cerebral vasodilatation in patients with arteriosclerosis may occur only in the less diseased vessels, thus compromising even more the circulation through the most extensively

involved vessels. Unfortunately, this hypothesis has not yet been scientifically tested. Those studies which have been done do indicate, however, that so far as over-all brain circulation and metabolism are concerned, normal middle aged and elderly subjects differ from those with clinical evidence of cerebral vascular disease only in the chance location of an atheromatous or occlusive lesion, with resulting neurologic signs. This particular concept has been previously expressed by Gould with respect to vascular disease of other organs.[40]

2. *The Influence of the Nervous Innervation of the Cerebral Vessels on Cerebral Vascular Resistance.* The sympathetic innervation of blood vessels in most parts of the body plays a significant role in the coarse regulation of blood flow into the part. A physiologic principle pertinent to one organ cannot, however, always be applied with validity to another. The true part which the autonomic nervous system plays in the control of cerebral circulation has not yet been entirely elucidated, although many clinicians have felt that removing or inhibiting the influence, whatever it may be, of the cervical sympathetic chain on the cerebral vessels will provide cerebral vasodilatation.

Unfortunately, many of the significant observations bearing on this problem have been made in animals and may not be applicable to man. In 1925, following direct microscopic observations of the pial vessels of the cat, rabbit and monkey, Florey came to the conclusion that he could see no constriction or dilatation of these vessels when the sympathetic ganglia in the neck were stimulated or cut. Nor did he observe any change in vessel caliber on stimulation of the vagus center in the medulla.[41] Three years later Forbes and Wolff recorded slightly different results from stimulation of the cervical sympathetic nerve in cat, dogs and monkeys.[42] Although they observed constriction of the pial arteries, the amount was small, averaging only 8% of original total diameter, whereas the corresponding constriction in dural vessels was about 30%, and in skin vessels, more than 80%. They saw no dilatation when the sympathetics were cut or removed. Studies by Penfield [43] and Chrobski and Penfield [44] demonstrated the presence of nerves innervating arteries larger than 50 μ throughout the central nervous system, and noted that complete removal of all the sympathetic nerve fibers which enter the cranial cavity on the carotid and vertebral arteries did not appreciably reduce the number of normal intracranial perivascular nerve fibers. Sectioning the great superficial petrosal nerve, thought to carry vasodilator fibers of parasympathetic origin to the brain vessels, as well as the sympathetic nerves, did not denervate the cerebral vessels. The true function of the innervation of the intracerebral vessels therefore remains unexplained.

These studies suggest that the sympathetic nervous system does not greatly influence cerebral vascular resistance or blood flow. Additional observations confirm this impression. The constancy of cerebral blood

flow in the same individual,[8, 45] as opposed to the extreme variability of blood flow to areas known to be under sympathetic control, also suggests the lack of sympathetic influence on cerebral circulation. Stellate ganglion block by procaine infiltration does not increase cerebral blood flow or decrease cerebral vascular resistance in normal subjects, in patients with hypertension, or in patients with known cerebral vascular disease.[46, 30] Such studies have not been done in young persons following acute brain embolism, which conceivably could produce vascular spasm, as was experimentally produced in animals by Villaret and Cachera.[47] Such increased vascular tone might be altered by sympathetic block, but this must await laboratory demonstration.

Administration of drugs known to block sympathetic activity at different sites has not increased cerebral blood flow, and vascular resistance diminishes only in proportion to the drop in blood pressure.[13, 15, 16] Studies in animals indicate that tetraethylammonium bromide does not prevent fall in cerebral blood flow as blood pressure is reduced.[9] This is additional evidence against the nervous regulation of cerebral circulation.

There are many clinical studies purporting to show the effects of stellate ganglion block on acute and chronic cerebral vascular lesions. Of these, the only one which can be said to have been controlled is that of Millikan, Lundy and Smith,[48] who found no effect from this procedure.

Though it is not known whether the effects of emotional stress or apprehension on cerebral circulation can justifiably be discussed under nervous control of cerebral circulation, comments on this problem are as appropriate here as anywhere. There is fairly widespread belief in clinical circles that periods of emotional stress may precipitate cerebral vascular lesions, both infarction and hemorrhage, although clinical demonstration of this has been unconvincing.[49] The possible physiologic mechanism whereby such a relationship might occur has never been fully explained, though possible further elevation of arterial pressure by anger in a hypertensive patient conceivably could result in an increase in cerebral vascular resistance and vascular tone to the point of injury to the vessel itself. Apprehension actually has so many different physiologic manifestations that it cannot be discussed briefly or simply, but in a group of normal young men apprehension induced by implied possible harm during the blood flow procedure, and manifested by tachycardia, widened pulse pressure, sweating and paleness, did not change cerebral blood flow, oxygen consumption or vascular resistance.[8] Nothing has yet appeared in the literature which justifies discarding this evidence.

3. *Blood Viscosity and Coagulability, Intracranial Pressure and Venous Pressure.* The classic situation in which blood viscosity is increased is polycythemia. It is recognized that patients with polycythemia vera have an increased incidence of recurrent focal cerebral ischemic attacks and of actual brain infarction. The precise mechanism for this has never been

fully established because the processes whereby polycythemia encourages intravascular clotting are not altogether clarified. It has been demonstrated by Kety,[50] however, that in polycythemia vera the cerebral blood flow is greatly reduced and cerebral vascular resistance correspondingly increased. The high oxygen-carrying capacity of the blood may prevent signs of cerebral ischemia in such patients despite the markedly reduced blood flow, but it is reasonable to assume that there is a relationship between the decreased blood flow and the increased incidence of cerebral infarction in this condition.

The opposite situation obtains in severe anemias, in which cerebral vascular resistance is decreased, blood flow increased and cerebral metabolism reduced.[51, 52] It should be emphasized that this applies only to chronic anemias, for acute blood loss produces alterations in arterial pressure which vitiate any controlled observation on the effects of acute anemia per se. The cerebral vasodilatation which occurs in chronic anemia may be partially the result of diminished blood viscosity or decreased arterial oxygen tension. The circulatory effects of anemia do not appear until hemoglobin values have fallen to about 50% of normal; at this point cardiac output is increased in about the same proportion as is cerebral blood flow,[53] so that the circulatory results of chronic anemia may have nothing to do with blood viscosity, but rather be a compensatory effort on the part of whole organism in response to diminished tissue oxygen.

At present no information is available on the effects on cerebral circulation and metabolism of altering blood coagulability by means of anticoagulant medication, except for one small series of observations on the effect of heparin on cerebral circulation in elderly patients. These individuals showed no alterations in cerebral circulation on heparin.[54] The recent clinical observations on the effects of Dicumarol on impending cerebral vascular thrombosis [3, 4] indicate the necessity for further studies in this field, particularly since the means by which anticoagulants produce their beneficial effect is not yet known.

Alterations in intracranial pressure probably have little influence on the problem of cerebral vascular disease. It has been demonstrated that cerebral blood flow is decreased in proportion to the increase of intracranial pressure in brain tumor.[55] Venous pressure is of course increased in congestive heart failure, and theoretically this might provide resistance to egress of blood from the brain. The decrease in cerebral blood flow which occurs in heart failure [29] may be due to the accompanying decrease in cardiac output and have no relation to venous pressure. It is of interest that there is no increased incidence of cerebral vascular thrombosis in patients with low output heart failure, despite the diminished cerebral blood flow in this condition. Indeed, increase in venous pressure seems to have little effect on the brain clinically or pathologically, unless the elevation of pressure is extreme and prolonged, as in strangulation.

4. *The Effects on Cerebral Vessels of Chemical Substances in the Blood.* The effect of chemical substances on the cerebral vessels constitutes the

most important device in the regulation of cerebral circulation. This regulatory mechanism is, however, complicated and apparently inconsistent, and how it may pertain to a better understanding of the pathogenesis and treatment of vascular disease of the brain is not yet understood. For many years one of the paramount objectives in the treatment of cerebral vascular thrombosis with infarction has been to produce cerebral vasodilatation in the hope that increasing the blood flow to the damaged area might minimize the extent of the damage and also promote the development of collateral circulation. To that end many drugs have been used in the treatment of acute and chronic cerebral vascular lesions. The great majority of these drugs do not, in fact, provide cerebral vasodilatation, and it is questionable that it would be of any value if they did. There is no evidence which demonstrates the clinical efficacy in cerebral vascular disease of even the proved cerebral vasodilators. Studies have demonstrated that increasing arterial carbon dioxide tension by inhalation of 5 to 7% carbon dioxide results in a 75% increase in cerebral blood flow in normal young men,[56] much less in the elderly subject.[39] Reduction of arterial carbon dioxide content results in decrease in cerebral blood during hyperventilation.[57] Changes in hydrogen ion content of the blood were also in direct relationship to changes in blood flow in these studies. Since carbon dioxide tension and hydrogen ion content increase above normal in infarcted tissue, it would seem reasonable to believe that the infarction itself has already provided the stimulus for maximal local vasodilatation; one wonders if the use of cerebral vasodilators may not actually direct blood away from the needy area. It is also recognized that decreasing the oxygen content and tension of the blood produces cerebral vasodilatation,[56] and since anoxia occurs almost instantaneously in infarcted tissue, it again seems that the stimulus for increasing blood flow locally is already present. In such circumstances as acute embolism to a brain artery, the use of cerebral vasodilators may conceivably relax the spasm of the vessels which may occur distal to point at which the embolism lodges. There is little clinical evidence on this point.

What has already been mentioned is only a fragment of the picture of chemical control of the cerebral circulation. It has been demonstrated that cerebral vascular resistance may be decreased in the presence of an increased [58] or decreased [59] blood carbon dioxide content, an increased [58] or decreased [56] blood pH, and an increased,[56] unchanged [60] or decreased [59] arterial carbon dioxide tension.

Of the various drugs used in the treatment of cerebral vascular lesions, only papaverine [61] and carbon dioxide by inhalation actually produce vasodilatation. Histamine,[62] procaine intravenously,[63] Priscoline,[64] nicotinic acid [65] and ethyl alcohol [66] have no effect on cerebral blood flow, and there is serious doubt that they could influence the course of cerebral vascular disease. Aminophylline results in constriction of cerebral vessels and reduced cerebral blood flow.[67]

5. *Local Brain Tissue Requirements.* The ability of the brain to alter

local blood supply according to the needs of the tissues would appear to be one of the most important factors in the regulation of cerebral circulation as it pertains to the problem of cerebral vascular disease. If such a regulatory mechanism is present and effective, one could anticipate that local deprivation of blood flow—as in thrombosis or embolism of a cerebral vessel—would provide the maximal stimulus for increasing local circulation. There is ample evidence that such a local regulating mechanism is present in the brain. In cats, light thrown on the retina increases blood flow as recorded thermo-electrically in the occipital cortex.[68] It is also known that anoxia increases cerebral blood flow,[56] and studies on the brains of monkeys with the technic of polarography have indicated that a form of "reactive hyperemia" also occurs in the brain.[69] This phenomenon has long been thought to be a compensatory dilatation of blood vessels in response to temporarily induced ischemia. Observations on patients with myxedema also indicate that cerebral blood flow is reduced as the need of the tissue for oxygen and glucose is diminished,[70] and recent studies on the effects of hypothermia on the extent of induced cerebral infarction in dogs confirm the impression that, if local tissue metabolic requirements are reduced simultaneously with the cessation of blood flow to a part of the brain, the extent of the ensuing infarction will be much less than if tissue requirements are normal.[71] Further research in this field is needed, for there is little evidence yet available to suggest that cerebral vasodilators are of any value in minimizing an area of infarction; perhaps a more logical clinical approach would be to lower the metabolic needs of the damaged brain tissue, as by hypothermia, in an effort to reduce the area of tissue necrosis as much as possible.

It is apparent that much can be learned of the nature of cerebral vascular disease by careful application of facts gleaned from studies of the physiology of the circulation and metabolism of the human brain. Further studies are needed to clarify the mechanisms which result in thrombus formation and to depict more clearly the circulation in individual parts of the brain. Some of this information must await a suitable tool for the measurement of regional cerebral blood flow.

Summario in Interlingua

Un fundo considerabile de informationes ha essite accumulate in recente annos con respecto al physiologia del circulation cerebral, e multo de iste fundo pare illuminar, in terminos theoric, le problema clinic de morbo cerebro-vascular. Es discutite le varie factores pro le quales il ha essite demonstrate que illos influentia le fluxo de sanguine cerebral, le metabolismo cerebral, e le resistentia cerebro-vascular, e le correlation del information physiologic con le problemas clinic es tentate. Le effective pression arterial es un del plus importante variabiles que exerce un influentia super le circulation cerebral. Le effectos de hypertension e de hypotension es discutite, tanto ab le puncto de vista del physiologia del circulation cerebral como etiam in lor signification pro morbos cerebro-vascular.

Es etiam discutite, individualmente e in detalio, le varie factores que constitue le resistentia cerebro-vascular. Iste factores include (1) invetulation, arteriosclero-

sis cerebral, e altere cambiamentos organic in le vasos cerebral; (2) le influentia del innervation del vasos cerebral super le resistentia cerebro-vascular; (3) viscositate e coagulabilitate del sanguine, pression intracranial, e pression venose; (4) le effectos producite in le vasos cerebral per substantias chimic in le sanguine; e (5) requirimentos local del histos cerebral. Le studio physiologic de omne iste variabiles ha promovite le comprension de morbo cerebro-vascular, tanto acute como etiam chronic.

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ACUTE RHEUMATIC FEVER: A STUDY OF 132 CASES IN YOUNG ADULTS *

By RICHARD C. BATES, M.D., F.A.C.P., *Lansing, Michigan*

THE changing lights cast by new diagnostic aids and better therapy require that the classic concepts of the clinical picture of a disease be re-examined from time to time. The knowledge that rheumatic fever is always a sequel to a streptococcal infection, and that penicillin may prevent the disease [1] and prevent reinfections resulting in recurrent attacks,[2] should result in better mortality and morbidity statistics in the future. It seems likely, too, that prompt eradication of streptococci from patients with acute rheumatic fever may alter the familiar chronicity of the disease, as well as modify the severity of the attack. In this regard, the previously accepted doctrine of prolonged and strict bed-rest may be changed, since the relapses previously observed with resumption of activity may have resulted from exposure to new infections, rather than from a recrudescence of inapparent disease.

The development of new laboratory methods for detecting antibodies from the previous streptococcal infection, such as determination of the anti-streptolysin "O" titer, and new tests for inflammation such as the C-reactive protein,[3] diphenylamine,[4] and sialic acid tests,[5] have permitted more accurate diagnoses and better means of gauging activity than heretofore. These, too, will alter previous concepts.

We wish to report the clinical manifestations of acute rheumatic fever in 132 males in military service studied and treated in the period from December, 1944, to May, 1956, at the Great Lakes Naval Hospital, Great Lakes, Illinois. One of the best opportunities to observe the acute stages of rheumatic fever is provided in military service, where physical examinations have preceded the onset of illness in every instance, detection is early because of a high incidence of cases occurring in epidemics, and the environment, sex and age groups are uniform. Streptococcal epidemics and subsequent epidemics of acute rheumatic fever were extensively studied in similar military groups during the Second World War.[6, 7]

It is doubtful whether, with present methods for detection, any series of cases can be obtained that are diagnosed and placed under treatment in a shorter time than were those reported here. Studies have shown that the incidence of permanent valvular damage seems to increase when therapy is delayed.[8, 9] These cases, then, may represent the lowest morbidity that may be expected in this age group under present treatment régimes.

* Received for publication March 22, 1957.

Requests for reprints should be addressed to Richard C. Bates, M.D., 1820 East Michigan Avenue, Lansing 12, Michigan.

Material and Methods

Table 1 records the age spread, length of time in service, and periods elapsing between the onset of respiratory infection and the onset of sore joints, and those between joint pains and admission to the hospital. Five cases occurred in Negroes, four in patients of Spanish extraction, and the

Table 1

A. Ages of the subjects in this study.

Age	Number
17	46
18	42
19	17
20	11
21	4
22	6
23	3
24	2
28	1

B. Length of time in service to the onset of sore joints, in days (81 cases recorded).

Days	Number
0–9	2
10–19	3
20–29	6
30–39	15
40–49	13
50–59	15
60–69	16
70–79	5
80–89	3
90–99	1
Over 100	2

C. Length of time in days between onset of upper respiratory infection and onset of sore joints (92 cases recorded). Mean, 16.2 days.

Days	Number
0– 6	21
7–13	23
14–20	28
21–27	10
Over 27	10

D. Length of time between onset of sore joints and admission to the hospital in days. Mean, 4.9 days.

Days	Number	Days	Number
0	11	11–14	11
1– 2	42	15–19	3
3– 6	46	20–29	4
7–10	14	30–39	1

remainder in patients of other European extraction. All cases were originally seen at their dispensary and referred to the hospital for admission.

As soon as possible after admission, usually within an hour, examination was carried out by the author and an electrocardiogram obtained. Laboratory studies other than the electrocardiogram were obtained the following

morning. Heart sounds were evaluated on rounds daily for the first week, and at least at weekly intervals thereafter. Chest x-rays were obtained within three days of admission. Sedimentation rates, C-reactive protein determinations, electrocardiograms and diphenylamine and/or sialic acid determinations were obtained at weekly intervals throughout the entire hospital stay.

All findings were recorded on a special summary sheet on the front of each chart on daily rounds, and data obtained from these sheets form the basis for the statistics herein presented.

On admission, each patient was placed on bed-rest and started on 300,000 units of procaine penicillin G intramuscularly daily for 10 days to eliminate streptococci, followed by 1.0 gm. of sulfisoxazole (Gantrisin) daily to prevent reinfection. As soon as the diagnosis was made, in agreement with the criteria of Jones as recently modified,[10] treatment was begun with aspirin in divided doses totaling 6.0 gm. daily for the first two days, and 4.0 gm. daily thereafter. In cases with carditis, cortisone was given in addition to aspirin, in a dose of 300 mg. the first day and 200 mg. daily thereafter until all manifestations apparent at the bedside had subsided, followed by a gradual reduction in dosage over the next three or four weeks. (While it was recognized that cortisone alone has not been proved to be of greater value than aspirin alone in the prevention of permanent heart damage,[11] definitive studies of the two drugs used together have not been reported.)

At the end of four weeks, or when the sedimentation rate had returned to normal, whichever occurred last, aspirin therapy was reduced in a period of from three to seven days and activity was initiated. By the end of the fifth week, if evidence of relapse had not occurred and the sedimentation rate was normal, aspirin was discontinued and the patient was assigned strenuous work, such as mopping floors, for from four to six hours daily. By the end of the sixth week, if evidence of reactivation was still absent, he was returned to full duty if the heart was normal, or processed for discharge from service if it was not. If objective evidence of reactivation (sore joints, fever, tachycardia) occurred at any time, bed-rest and medication as above were re-initiated. Since a few days elapsed between discharge and actual departure of the patient, each case was observed for about 10 days after withdrawal of medication and after resumption of strenuous physical activity.

Results

The occurrence of the clinical manifestations of acute rheumatic fever in these patients is presented in table 2, divided into major and minor criteria for the diagnosis, and comparison is made with data from other reports where available. Notable was the complete absence of chorea, heart failure, cardiac enlargement clinically or by x-ray examination, or deaths. In contrast to other reported series, all of our patients had objective arthritis at some time during their course. Since each was referred by a physician at

the dispensary level, this suggests that the diagnosis of rheumatic fever was not entertained unless arthritis occurred. Also, pediatric rheumatic fever is often manifested first by chorea, a rare occurrence in our age group. One patient each was admitted for backache, erythema marginatum and abdominal pain, but each subsequently developed arthritis. Other manifestations of rheumatic fever were anemia in 18.2%, albuminuria in 8.3%, pulmonary infiltration in four cases, abdominal pain in three cases, and a pericardial rub in one case. Petechiae occurred in six cases, erythema nodosum in two and herpes simplex in one.

TABLE 2

The Manifestations of Acute Rheumatic Fever: Comparison of Various Reports

Authors	Military Group				All Ages			Under 17
	Bates	Carmichael[12]	Gray[13]	Coburn[14]	Lieber and Holoubek[15]	Bruce[16]	Bland and Jones[17]	U. K. U. S.[11]
No. of Cases	132	302	158	65	162	386	1,000	497
Major Manifestations								
Carditis	56.1%				56.2	38.0		76.4
Arthritis	100.0				63.6	76.1	41.0	43.3
Chorea	0.0		1.3	1.5	9.3	3.5	51.8	10.9
Nodules	0.7			3.0	3.1	6.5	8.8	14.3
Erythema marginatum	9.1		1.9	7.7	0.6	9.5	7.1	5.8
Minor Manifestations								
Fever	56.8				88.3			
Arthralgia							40.1	
P-R interval	52.1			26.0	17.9			
Inflammation:								
ESR, DPA, SiA	100.0				85.8			
Leukocytosis	56.8							
CRP	86.1							
Preceding streptococcal infection								
History of respiratory infection	73.0	74.5	64.6	80.0	56.2			
ASO over 200	82.0							
Previous rheumatic fever	15.1	22.5	18.9		39.5			

Table 3 presents data on those patients with persistence of organic heart murmurs to the time of disposition, and attempts are made to correlate fever, previous attacks, erythema marginatum, anemia, recurrence of rheumatic activity after cessation of therapy, and leukocytosis. Statistical analyses by the Chi-square method show probabilities of chance alone causing these associations to be greater than 5% in each category, the most significant association being that with fever. Flare-up of rheumatic activity after cessation of therapy was among the least significant of any of these factors, and three of four patients with almost continuous rheumatic activity for over 100 days escaped without detectable heart damage and were eventually returned to duty.

TABLE 3

Correlation of Permanent Valvulitis with Other Phenomena

	No. With Valvulitis	No. Without	Totals	Chi^2	p Value
Fever over 100°					
With	26	49	75		
Without	11	46	57	3.826	>.05
Previous rheumatic fever					
With	9	11	20		
Without	28	84	112	3.378	.07
Erythema marginatum					
With	6	6	12		
Without	29	91	120	3.054	.08
Anemia (less than 12.8 gm. Hgb.)					
With	4	20	24		
Without	33	75	108	1.844	.18
Renewed activity after cessation of therapy					
With	14	28	42		
Without	23	67	90	.837	.45
Leukocytosis (over 10,000 WBC/mm.^{3})					
With	22	53	75		
Without	15	42	57	.153	.65

Table 4 indicates the time of appearance of murmurs in relation to admission to the hospital. Almost two thirds of the murmurs were present on admission, despite the brief period between onset of symptoms and admission in most cases. Only one murmur appeared with a "flare" that had not been previously heard. Renewed rheumatic activity after cessation of therapy occurred once in 35 cases, twice in three cases, and three times in four cases, for a total of 42 cases, or 31.8% of the entire group.

The mean duration of hospitalization was 52.1 days, but the curve was skewed by a few cases of unusually prolonged duration. Actually, 72.8% of the cases were hospitalized less than 60 days. Since a patient in military service is hospitalized until he is able to return to full duty, these periods represent the total duration of disability. The mean of 52 days amounts to only half that reported recently by Carmichael in his series.[12]

Fifteen patients had had one previous attack of rheumatic fever; two had

TABLE 4

Appearance of Murmurs From the Onset of Sore Joints

	Persistent Murmurs	Transient Murmurs	Totals
On admission	22	22	44
During the first week	5	6	11
Second week	4	3	7
Third week	2	1	3
Fourth week	1	1	2
Fifth week	0	0	0
Sixth week	1	0	1

TABLE 5

Observed Electrocardiographic Abnormalities *

P-R interval .20 or over	52 (39.4%)
Interference dissociation	5
ST-T wave changes	4
Complete heart block	3
A-V nodal rhythm	3
Frequent ventricular premature beats	2
Wenckebach's phenomenon	2
Second degree heart block	1
	72 (54.5%)

* In cases that regressed from one form of heart block to another, only the more complete form of the block is tabulated.

had two previous attacks, and three had had three previous attacks, a total of 20 patients, or 15.1% of the group.

A positive family history for rheumatic fever in close relatives (parents or siblings) was obtained in 22 instances, or 16.7%.

The presence of a constitutional factor in the determination of susceptibility to rheumatic fever has been debated.[18] Although we have been unable to obtain figures on a comparable group of controls, of 75 patients who were particularly examined and questioned, 60% had blue eyes themselves, and another 15% had immediate members of their families who were blue-eyed. The occurrence of red hair was noted in only seven members of the entire group.

Table 5 lists the electrocardiographic changes which were observed. Interference dissociation deserves special mention as being a highly specific electrocardiographic manifestation of rheumatic fever.

Table 6 gives the types and occurrence of transient and persistent organic murmurs which were observed. Persistent murmurs necessitating discharge from service occurred in 37 patients (28.0%). In comparison to this figure, Gardner[19] reported 57.5% of his series disabled in 1942, Gray[13] reported 20.2% in 1949, while Carmichael[12] reported that 40.3% of his cases observed between 1952 and 1955 were discharged from service because of cardiac disability.

TABLE 6

The Occurrence and Types of Organic Murmurs

	Transient Murmurs	Persistent Murmurs	Totals
Mitral systolic	29	24	53
Aortic systolic	17	18	35
Mitral diastolic	3	5	8
Aortic diastolic	1	7	8
Totals	50	54	104
Number of patients*	35	37	72

* More than one murmur occurred in some patients.

Discussion

These data tend to show that early concepts of rheumatic fever as a disease almost invariably associated with heart involvement [20] and with prolonged activity of the cardiac process necessitating months and years of bed-rest [21] require modification, at least in cases occurring after the age of 16. It has been observed [22, 23] that rheumatic fever tends to be milder when it occurs in the older age groups, as borne out by the absence in this series of congestive failure and progressive carditis leading to death.

Early teachings that premature physical activity leads to relapse, with further heart damage, cannot be substantiated. Indeed, almost all of the instances of valvulitis in these patients occurred very early in the course of their disease, preceding arthritis in some instances, we suspect. Such being the case, little hope can be held for any therapeutic measure to prevent rheumatic heart disease completely. Detailed analysis fails to correlate valvular damage with any of the factors of delay in treatment, previous attacks or clinical manifestations of the acute disease, which suggests that the occurrence of valvulitis may be independent of any other feature of the illness, perhaps related only to an individual susceptibility.

These observations might account for the failure of a recent large study to demonstrate the superiority in therapy of aspirin over steroid drugs, despite the general impression that steroids suppress the other clinical manifestations in a shorter time.[8, 11] If there are some patients whose hearts are immune to rheumatic inflammation, there might be others with susceptible hearts but resistant joints, which would account for the large numbers of older patients with rheumatic heart disease who cannot recall ever having had sore joints.

Rheumatic fever remains one of the few diseases for which complete bed-rest is still advised. As far as we can determine, this dictum, as in previous therapeutic regimens for postpartum, postoperative and myocardial infarction patients, rests more on theory than on controlled observation. Before penicillin was available it was noted that patients admitted to hospitals and convalescent homes tended to lose their streptococcal infections more readily than those left in home environments, a factor which may have accounted for continued rheumatic activity in the nonhospitalized, and the impression that bed-rest was essential. Further, it was thought that exercise, by increasing the work-load of the heart, would result in permanent "strain" of that organ. To substantiate these concepts it was pointed out that the left side of the heart performs more work than the right, and the left valves are those most frequently involved. Such concepts appear physiologically and pathologically unsound. While it seems reasonable that a patient with tachycardia, fever or changing murmurs, and certainly the patient with heart failure, should be restricted in activity, a well controlled, prolonged study is needed to prove that strict bed-rest, once these features

have subsided, has any bearing on the final outcome of the heart valves. While it would take a much longer period of observation than was available to us to determine the final outcome of these cases, in the period during which they were observed no evidence was found that rapid resumption of physical activity was harmful once the acute process had subsided.

Summary

The clinical features of 132 cases of acute rheumatic fever occurring in men in military service are presented and compared with previous reports.

Prompt diagnosis and hospitalization, with early penicillin abolition of streptococci, resulted in a more benign course of the disease and a shorter period of disability, but did not materially reduce the incidence of valvulitis. Attempts to identify features of the illness that accompany valvulitis were unrewarding, and valvulitis was found to be a very early feature of the disease in most instances. These observations lead us to suggest that valvulitis may be entirely separate from all other clinical features of rheumatic fever, and may not be entirely prevented by any currently known method of therapy.

No evidence was found that bed-rest beyond the period of acute carditis is of any value in determining the final outcome, or that prolonged rheumatic activity leads to greater heart damage in patients in this age group.

Summario in Interlingua

Es presentate analyses detaliate del aspectos clinic de acute febre rheumatic occurrente in 132 homines in le servicio militar. Iste casos esseva placiate sub tractamento un brevissime tempore post le declaration de dolores articular. Proque le majoritate del patientes habeva recentemente habite examines physic, il pote esser presumite que paucos habeva grados significative de morbo valvular ante le currente attacco de febre rheumatic.

Es presentate e comparate con previe reportos in le litteratura: datos relative al incidentia de attaccos antecedente, al historia familial con respecto a febre rheumatic, al presentia de factores constitutional, al constatationes clinic, electrocardiographic, e laboratorial, al relation chronologic inter entrata in le servicio militar, le declaration de infection respiratori, le manifestation de dolores articular, e le hospitalisation, e al occurrentia de permanente e transiente murmures.

In general, le morbo esseva benigne in iste casos. Le serie includeva ni morte ni disfallimento cardiac. Tamen, observationes notabile esseva le alte incidentia de valvulitis in despecto del melior therapia possibile secundo le standards currente e le manco de correlation inter le occurrentia de valvulitis e altere manifestationes del morbo.

Es formulate le opinion que valvulitis es possibilemente un phenomeno independente in febre rheumatic (relationate a illo solmente per le susceptibilitate del individuo), que illo pote preceder le declaration de dolores articular in multe casos, e que illo non es prevenibile per le currente methodos de tractamento. In le lumine de iste constatationes le necessitate de un prolongate allectamento in iste gruppo de etate (post que le plus acute aspectos del morbo ha subsidite) pare esser questionabile.

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PALMAR ERYTHEMA AND SPIDER ANGIOMATA IN RHEUMATOID ARTHRITIS *

By JOHN H. BLAND, M.D., F.A.C.P., *Burlington, Vermont,* ROBERT O'BRIEN, M.D., *Winooski, Vermont,* and RICHARD E. BOUCHARD, M.D., *Burlington, Vermont*

SAVE for the extensive observations and investigations of Dr. William B. Bean, the physical signs of palmar erythema and spider angiomata have received little clinical attention or interpretation. The forces producing them remain obscure. Their possible significance in diagnosis and therapy is an interesting, if diminutive, field for speculation.

Their appearance in a variety of disease states as well as in physiologic conditions—namely, pregnancy and normal aging—makes their observation and study a worth while project. They may provide foundation for important research; their proper interpretation currently has clinical usefulness. Spider angiomata have been most noted in chronic liver disease. Palmar erythema has the synonym, "liver palms." This suggests that observers have believed the lesions to be produced by forces residing in or related to the liver. We have observed both physical signs in a wide diversity of disease states. Clinical relationships lead us to believe that forces producing them arise from one of the integrative systems, more specifically, endocrine forces.

It should be stated that spider angiomata and palmar erythema have been occasionally seen in otherwise normal people. They seem to be of clinical significance only if new lesions appear or old ones enlarge, or if they are very numerous. We have observed them in one instance to come and go over areas of exposure such as arms, V of neck and backs of the hands.

The significance of these vascular changes in the skin is unknown. Do they represent local changes in the skin vessels? Or are they the small segment of the iceberg that can be seen, the preponderating remainder being a generalized change in the vascular system in response to certain unidentified endocrine forces?

Following the lead of Dr. Bean, one of us (J. H. B.) in 1950 began to make observations of vascular skin lesions. Particular emphasis was placed on palmar erythema and spider angiomata. Some data herein reported are from these observations, particularly those related to pregnancy, aging and rheumatoid arthritis. It became apparent that a systematic series of observations in rheumatoid arthritis would be a worthwhile study. Hence, on July 1, 1955, criteria for identification of palmar erythema and spider

* Received for publication February 23, 1957.
From the University of Vermont College of Medicine.
Requests for reprints should be addressed to John H. Bland, M.D., 376 College Street, Burlington, Vermont.

angiomata were agreed upon. Three observers examined patients in their offices, in a clinic devoted largely to rheumatic disease, and on the wards of two university teaching hospitals. Conditions of lighting were kept constant. A record was kept of the presence or absence of palmar erythema and spider angiomata. The criteria noted below were used in all instances.

Description of the Lesions and Criteria for Identification

Palmar Erythema: True palmar erythema can be identified if the following criteria are present:

The area of most intense redness is over the hypothenar eminence. The earliest evidence is in the proximal portion; it gradually extends distally. The next most common area is the central aspect of the thenar eminence. One notes a relative central pallor in the palm. With lesions of greater intensity there may be red areas or spots where the fingers join the palms between the palmar calluses. The palmar surface of fingertips is commonly red. With extreme palmar erythema the process extends to the dorsum of the fingertips in a horseshoe-like pattern at the base of the nails. There is a sharp line of demarcation between the red and the uninvolved skin.

Palmar erythema should be carefully differentiated from the normal diffuse mottled erythema involving the entire palmar surface, with a speckling of pale areas a millimeter or more in diameter. This varies in intensity and is correlated closely with emotional states, elevation or dependency of the hand, atmospheric temperature or pressure on the palm. True palmar erythema is not influenced by these factors but remains relatively constant. The term palmar erythema is reserved for the lesion of the thenar and hypothenar eminences with relative central palmar pallor.

Spider Angiomata: This lesion has been more definitively delineated than has palmar erythema. Three features characterize the spider: a body, legs, and surrounding erythema. It may vary in diameter from 1 mm. to 2 or 3 cm. in diameter. The body constitutes a central punctum or eminence. In small or early lesions this constitutes the only abnormality. Large spiders may have their central punctum projecting 1 mm. or more above the surface of the surrounding skin. Pulsations may be felt if they are of sufficient size. Branching legs radiate away from the central area (body), decreasing in size toward the periphery. The area encompassed by the legs is redder than the surrounding skin. Erythema may occur with few or no visible branching legs. Due to the local increase in arterial blood supply, skin temperature over a spider angioma is higher than that of the surrounding skin.[6] Blood flows from the body toward the periphery. This can be demonstrated by pressure over the central area with a blunt pencil lead, following which pallor appears; refilling and a blush of red follow release of pressure. Gently pressing a glass slide with release over the area also illustrates this.

Lesions rarely occur other than over the upper parts of the body, with

the face, neck, upper chest and arms most frequently affected. We found as the study progressed that we could detect much smaller lesions. Occasionally the earliest lesions showed a single small red spot surrounded by an anemic halo; later the central punctum grew larger, and radiating vascular strands appeared and extended in a centrifugal direction.

It became apparent that varying magnitudes of both lesions existed and grading was begun. A 1 plus was readily recognizable and fulfilled the criteria for palmar erythema or spider angioma; a 4 plus palmar erythema was bright red and had marked central pallor, and there were lesions at the bases of the fingers, pads of fingers and about the nails; a 4 plus spider angioma showed visible pulsation with a hand lens, and had a raised central punctum and many obvious "legs" radiating from it.

Aims of the Study

1. To establish incidence of palmar erythema and spider angiomata in rheumatoid arthritis.
2. To speculate, on the basis of our data and those of Bean [4-11] and others, what the forces are that produce palmar erythema.
3. To speculate on clinical interpretation of the lesions in normal or abnormal states.
4. To correlate with total protein and albumin and globulin concentrations in the serum.
5. To determine its usefulness, if any, as a physical sign in rheumatoid arthritis as well as in other disease states.

Incidence in Rheumatoid Arthritis and Normal Pregnancy

We examined 152 patients with obvious, established rheumatoid arthritis and found that 94 (or 61%) manifested palmar erythema. Of 152 patients, 12 (or 7.7%) manifested spider angiomata. A further breakdown of the figures was made between patients with peripheral rheumatoid arthritis and those with rheumatoid spondylitis, assuming that these constitute the same disease. There were 137 patients with peripheral rheumatoid arthritis, 87 (or 63%) of whom had palmar erythema; 11 (or 7.9%) had spider angiomata. There were 15 patients with rheumatoid spondylitis, seven (about 50%) of whom had palmar erythema; one (or 6.6%) had spider angiomata.

One author (J. H. B.) over a two and one-half year period observed 148 pregnant white women and found an incidence of 52% with palmar erythema. All subjects were in the third trimester of pregnancy. No conclusions can be reached as to when the lesions appeared during pregnancy. No data are available in this study regarding whether they disappeared following delivery. Spider angiomata were not sought for, and constitute a further study, along with extension of the study of palmar erythema. Bean et al.[5] found an incidence of 62.5% for palmar erythema and 66.6% for

spider angiomata in observations on 486 pregnant white women. Both palmar erythema and spider angiomata tended to disappear post partum. The most rapid rate of disappearance or diminution in size was during the first week post partum. This continued at a more gradual rate thereafter. No definitive information is available on ultimate disappearance. A few of their patients showed decrease in size or disappearance of the lesions during the few weeks preceding delivery.

A total of 52 patients with a variety of disease states, all of whom manifested either palmar erythema or spider angiomata, or both, had total serum protein and albumin and globulin concentrations examined. Of these, 88% showed alterations in the total protein concentration and an increase in globulin relative to albumin concentrations. This finding suggests that the forces leading to production of the lesions may be related to immunologic mechanisms associated with production of increased quantities of globulin or decreased albumin synthesis. Very few patients have been studied by electrophoretic pattern analysis. This constitutes a part of further study.

A number of observations of palmar erythema have been made in physiologic aging but not a statistically significant number, due to the difficulty in defining this state. It can be said that it frequently accompanies other signs of aging, such as osteoporosis, skin pigmentation and atrophy, arteriosclerosis, benign hypertension, wrinkling of the skin, gray hair and loss of muscle tone.

Discussion

Palmar erythema was first noted by Chalmers in 1899.[1] He carefully described the lesion occurring in Europeans living on the Gold Coast of West Africa. No symptoms were connected with it, and the author made no speculations on its cause. Lane in 1929 [2] studied this phenomenon in two men who had had palmar erythema as long as they could remember. Lane pointed out familial and hereditary features. Both spider angiomata and palmar erythema were noted in 1932 to be associated with liver disease.[3] Skin temperature in both lesions was established as being higher than that of the surrounding skin. A similar erythema of the soles has been noted. The lesions have been reported mainly in association with chronic liver disease, though they have been observed in such widely divergent disease states as tuberculosis and chronic nutritional states, normal pregnancy and chronic pulmonary disease, gall-bladder disease, acute infectious hepatitis, chronic constrictive pericarditis and hyperthyroidism.[4] Bean's classic papers [4, 5, 6, 7, 8, 9, 10, 11] and that by Walsh and Becker [12] should be reviewed by anyone who wishes a comprehensive grasp of the problem.

Certain speculations have been forthcoming regarding the forces leading to the production of spider angiomata and palmar erythema.[4, 6, 8] The frequent association of the two lesions, noted by Bean [4–11] and Walsh and Becker,[12] suggests that the causes leading to both may be the same or very similar. We can say from our study that palmar erythema may occur with-

out spider angiomata, but we have seen no patients who have spider angiomata without palmar erythema. They occur with greatest frequency in patients with liver disease of a wide variety of causes, such as portal cirrhosis, infectious hepatitis, "cardiac" cirrhosis, obstruction of bile duct with stone, primary hepatoma, carcinoma of the bowel with hepatic metatases, hemochromatosis and toxic hepatitis due to heavy metal poisoning. Generally, the more severe the liver disease, the greater the likelihood of developing the lesions. However, liver disease alone does not explain them, because many persons die of liver disease and never have them; also, they appear in many states which have no known associated liver dysfunction.

We became especially interested in these lesions as they occur in rheumatoid arthritis because of the well known ameliorating effect of jaundice or pregnancy on this disease. Palmar erythema and spider angiomata occur in all three conditions, suggesting that a similar mechanism may underlie this phenomenon of amelioration of rheumatoid arthritis and the emergence of these lesions. Because the lesions occurring in normal pregnancy disappear post partum, it seems justified to consider an endocrine mechanism, possibly utilizable in formulating endocrine etiology; a therapeutic avenue might be opened by such speculation.

A common denominator is the increase in circulating estrogen and related 17-ketosteroid hormones. An increase in estrogens is a well known normal phenomenon of pregnancy and occurs at about the same time the spider angiomata and palmar erythema make their appearance.[5] The liver normally destroys, changes or inactivates estrogens. It has been shown in some cases of portal cirrhosis that large quantities of estrogen are excreted in the urine, sometimes in unusual form. Could the causative factors of these skin lesions lie in prolonged alterations of circulating 17-ketosteroid hormones?

The acute action of estrogens upon the minute vessels of the ear in oophorectomized rabbits has been reported to cause dilation by Reynolds and Foster.[13] It is not unlikely that a protracted action might affect blood vessels throughout the body, as well as those of the female genital tract, which have been extensively investigated. The elongation and coiling of the spiral arteries of the endometrium suggest a morphologic similarity to the cutaneous spider, which is a small coiled end artery in the subcutaneous tissue. Edwards et al.[14] found the skin of castrate and eunuchoid men to be very pale and to contain little hemoglobin. Most of the hemoglobin in skin arteries was in the reduced state. When the endocrine disorder was ameliorated or corrected by androgen therapy there was a spectacular increase in the vascularity of the skin, with a preponderant rise in oxyhemoglobin. The skin of the hands and feet became distinctly red. This evidence provides more support for this speculation.

These observations and speculations suggest that the occurrence of spider angiomata and palmar erythema may be related to an abnormality in the metabolism of 17-ketosteroid hormones, especially estrogens and androgens,

as originally postulated by Bean.[5, 6] It could be due to estrogenic substances acting directly on skin vessels, or be the consequence of an as yet undetermined endocrine abnormality related to estrogen and androgen.

Conclusions

1. In this study palmar erythema occurred in 61% of patients with established rheumatoid arthritis. This constitutes a sufficient number to make it an occasionally useful though nonspecific and minor physical sign of this disease in obscure cases.

2. Spider angiomata occurred in 7.7% of patients with established rheumatoid arthritis.

Further studies in progress are concerned with correlation of the lesions with intensity and duration of this disease, their incidence in physiologic aging, and with efforts to produce new lesions or accentuate old ones by estrogen administration.

Summario in Interlingua

Le fortias que produce le lesiones vasculo-cutanee "erythema palmar" e "nevo aranee" es incognoscite. Lor interpretation clinic es obscur. Le lesiones occurre in un varietate de statos pathologic e etiam in certe conditiones physiologic, como per exemplo pregnantia e invetulation normal.

Es stipulate criterios pro le identification de erythema palmar e nevo aranee. Cento cinquanta-duo patientes con establite e obvie arthritis rheumatoide esseva examinate, e il esseva trovate que 94 (i.e. 61%) manifestava erythema palmar e 12 (i.e. 7,7%) nevos aranee. Septe ex 15 patientes con spondylitis rheumatoide (i.e. 50%) habeva erythema palmar; solmente un habeva nevas aranee.

Cento quaranta-octo gravidas de racia blanc esseva examinate, e un incidentia de 52% de erythema palmar esseva constatate inter illas. Bean et al. trovava un incidentia de 62,5% de erythema palmar e de 66,6% de nevos aranee in le examine de 486 gravidas de racia blanc. In su studio, ambe lesiones tendeva a disparer post parto. Le plus rapide reduction del dimension del lesiones occurreva durante le prime septimana post parto. Postea le processo reductori continuava plus gradualmente. Le presente studio ha nihil a adder a iste observation. Es presentate un revista historic del observationes, speculationes, e conclusiones provisori in re le signification de iste lesiones.

Es discutite un hypothese—primo formulate per Bean—que erythema palmar e nevos aranee se disveloppa como responsa al stimulo de augmentate nivellos de circulante hormones steroide, plus specificamente de estrogeno o de alterate formas de estrogeno o androgeno. Erythema palmar es a vices utile como minor signo physic de arthritis rheumatoide.

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PERFORATION AND HEMORRHAGE FROM DUODENAL ULCER DURING THE ADMINISTRATION OF *RAUWOLFIA SERPENTINA:* REPORT OF FIVE CASES*

By Wilk O. West, M.D., *Charleston, West Virginia*

Introduction

Rauwolfia serpentina, or snakeroot, is a drug which has been used in Indian medicine for the past 30 centuries for a host of human maladies, including anxiety, snakebite, psychoses, epilepsy and insomnia. It was named after the German physician, Leonhard Rauwolf.

This agent has but recently (within the last three years) come into its own in this country, and has been a valuable adjunct in the treatment of hypertension [1-3] and emotional disorders.[4, 5] Most of the effects [1] and side-effects [6] of serpentina are well recognized, but probably are not appreciated to the fullest extent. Several disturbing reports have appeared in the literature recently concerning complications which have developed in patients taking the serpentina alkaloids.[7-10] Most of these were in psychiatric patients in larger hospitals. Physicians generally should become cognizant of these facts and the mechanisms involved so that they may be better armed to recognize and prevent their occurrences.

In our hospital, both oral and parenteral reserpine have been employed with a great deal of success in the treatment of severe hypertension, both alone and in combination with the more potent antihypertensives, in hypertensive emergencies and in psychoses secondary to myocardial infarction, cerebral vascular accidents, surgery, and various other forms of trauma. It was thought to be lifesaving in two recent cases of malignant hypertension with acute encephalopathy. We rarely use these preparations in the treatment of mild, labile, essential hypertension or tension states, since serious complications have developed in five patients who were taking these agents.

This report deals with five of the 42 cases of perforation and hemorrhage from duodenal ulcer occurring over the past one and one-half years at our 250-bed general hospital. All of these patients were taking *Rauwolfia serpentina* for hypertension when the complications developed.

Case Reports

Case 1. A 70 year old white male coal miner with a long history of hypertension was admitted to the medical service on February 11, 1956, with recurrent epistaxis.

* Received for publication April 9, 1957.

From the Department of Internal Medicine, Charleston Memorial Hospital, Charleston, West Virginia.

Requests for reprints should be addressed to Wilk O. West, M.D., Chief Medical Resident, Charleston Memorial Hospital, Box 3189, Charleston, West Virginia.

Physical examination was essentially negative except for a blood pressure of 220/130 mm. of Hg and bleeding from the right nostril. The bleeding was controlled by packing and the patient was placed on oral reserpine, 0.25 mg. four times a day.

Four days later the patient developed acute, severe epigastric pain, nausea and vomiting, and great apprehension. In spite of the negative x-ray findings, he was taken to surgery the following morning, where a perforated duodenal ulcer was discovered and a duodenorrhaphy performed. The postoperative course was uneventful and he was discharged on an ulcer regimen. Reserpine was discontinued.

Case 2. A 54 year old white male coal miner was admitted to the medical service on February 16, 1956. A diagnosis of subarachnoid hemorrhage was made. There was a long history of hypertension, and the blood pressure was 260/160 mm. of Hg. This patient had ulcer symptoms dating back many years, and there had been some question of a positive x-ray diagnosis of ulcer five years prior to admission.

Physical findings, aside from severe hypertension and papilledema, were confined to the neurologic. The patient was disoriented, confused and incoherent. There was weakness of the right extremities, with no other abnormal signs. Lumbar puncture on two occasions revealed gross blood. Routine laboratory studies were normal.

The patient seemed to improve under conservative therapy, but because of his confusion, agitation and hypertension was placed on parenteral and oral reserpine, on which he showed gradual improvement. On February 21, 1956, he was given prophylactic antacid therapy.

On March 1, 1956, 13 days after institution of reserpine therapy, an acute gastrointestinal hemorrhage occurred, as manifested by a fall in hemoglobin from 15 to 8 gm., melena, weakness and mild shock. An upper gastrointestinal series at this time revealed an active duodenal ulcer which evidently had been the site of bleeding. The patient was treated with repeated whole blood transfusions and ulcer therapy and responded well; reserpine was stopped. He was released against medical advice on March 8, 1956.

Case 3. A 53 year old white male dishwasher was admitted to the surgical service on August 28, 1956, complaining of severe epigastric pain. For some eight months prior to admission he had complained intermittently of gnawing epigastric pain, relieved by food and alkali. He had been treated for hypertension for approximately six months prior to admission. This treatment included some Rauwolfia alkaloid, type unknown, plus a low salt diet.

Physical examination revealed a blood pressure of 220/110 mm. of Hg and a temperature of 100° F. The heart and lungs were normal. The abdomen was slightly distended, and there was epigastric tenderness; bowel sounds were hyperactive. An upright film of the abdomen revealed free air under the diaphragm. The patient was taken to surgery, where a perforated duodenal ulcer was identified and duodenorrhaphy performed. The postoperative course was normal and the patient was discharged on an ulcer regimen. The antihypertensive agent was discontinued.

Case 4. A 54 year old white male gasoline station worker was admitted to the medical service on August 1, 1956, with a history of hematemesis and melena of several hours' duration. The patient had a past history suggesting peptic ulcer, and was a known hypertensive with coronary insufficiency. He had been taking Raudixin, 50 mg. four times a day, for over a year prior to admission.

Physical examination revealed a blood pressure of 210/100 mm. of Hg and tachycardia. The heart was enlarged and the lungs were clear. The abdomen was negative. The hemoglobin was 8.5 gm., rising and stabilizing at 10 gm. on August 3, 1956, with repeated whole blood transfusions. An upper gastrointestinal series the day following admission revealed the presence of a duodenal ulcer.

The patient did fairly well until August 6, 1956, when he developed acute left ventricular failure. The admission history had failed to bring out the fact that the

patient had had recent symptoms of cardiac failure. He was treated by rapid digitalization, aminophylline and mercurial diuretics. Despite this, and repeated blood transfusions, his condition deteriorated rapidly and on August 11, 1956, he was taken to surgery, where a prepyloric ulcer was identified and subtotal gastrectomy performed. This ulcer, however, was not found by the pathologist; the bleeding therefore could quite possibly have come from the duodenum. Postoperatively the patient did poorly, and died of circulatory failure later that same day.

Case 5. An 82 year old white housewife was admitted to the medical service on July 24, 1956, complaining of severe burning epigastric pain. She had noted tarry stools for the three days prior to this. Past history revealed symptoms of peptic ulcer over a two-year period prior to admission, although these had not been present for the last two months. Approximately seven days before the onset of the present illness the patient was given 1 Eskaserp spansule daily for long standing hypertension.

The blood pressure was 154/54 mm. of Hg, which was far lower than on outpatient determinations. There was significant epigastric tenderness. Laboratory studies were essentially normal except for a hemoglobin of 10.2 gm. An upper gastrointestinal series revealed the presence of an active duodenal ulcer and marked spasm of the duodenal cap. The patient was treated conservatively and discharged on an ulcer regimen. The serpentina alkaloid was stopped.

Discussion

Clark and Schneider [11] studied the effect of 1 mg. of intravenous reserpine on gastric acidity in 24 subjects, five of whom had peptic ulcer. Reserpine produced a significant rise in gastric acidity within 30 minutes of injection, and this was sustained over at least a four-hour period. The magnitude of increase was not influenced by the degree of base line acidity or by the presence of peptic ulcer. Eleven of these subjects were studied in the same manner, using saline placebos, and the changes were found not to be statistically significant. In a later study,[12] these workers showed that this effect was not significantly altered by the following therapeutic agents used intravenously: atropine, 0.3 mg.; Banthine, 50 mg.; and adrenalin, 1–1,000 0.3 c.c. They suggested that this action of reserpine was not central, but most probably peripheral or humoral.

Wofford and Cummins [7] reported a 46 year old psychiatric patient who developed acute bleeding from what was probably an old healed peptic ulcer four days after the daily oral administration of 4 mg. reserpine. The patient's uropepsin level increased markedly. This suggests a rise in gastric pepsin, which of course parallels changes in gastric acidity. The authors suggested that chlorpromazine might be the drug of choice in the psychiatric patient with peptic ulcer. It has been shown that this drug causes a decrease in gastric acidity.[13] Promazine and Compazine may also be used for the same reason. Hussar and Bruno [8] reported the development of peptic ulcer for the first time in three psychiatric patients during prolonged reserpine therapy. These cases were uncomplicated and required no surgery. Hollister [9] has recently reported four cases of gastrointestinal bleeding thought to be secondary to the administration of Rauwolfia alkaloids. Only one of these patients showed the presence of duodenal ulceration. Up-

per gastrointestinal series performed on the other three patients showed reflux esophagitis without ulceration, hiatal hernia without ulceration, and an unsatisfactory examination. Three of these patients were psychiatric and one was hypertensive. Dillon and Swain [10] also have described two cases of gastrointestinal bleeding as a complication of reserpine administration; both of these were psychiatric patients.

Drenick [14] recently reported that in a study of 13 cases, Serpasil, 0.25 mg. three times a day orally, did not influence the secretion of hydrochloric acid. Eight of these patients had duodenal ulcers, three had prepyloric ulcers, two peptic esophagitis with ulceration, and one gastritis. All patients were on a bland diet. Eight had been on antacids, and one had been on antacids and anticholinergic drugs before this study. Gastric analyses were performed before and during Serpasil administration. Most patients seemed to improve on this therapy. In all probability, during the time of Serpasil administration these patients were unconsciously more aware of their disease, and adhered more rigidly to their ulcer regimens.

Haverback and associates [15] have demonstrated that the daily administration of 1 mg. reserpine intramuscularly to man virtually depletes serotonin from platelets in one week. It was formerly thought that platelet serotonin played some part in the hemostatic mechanism and could for this reason possibly be related to the occurrence of peptic ulcer and its complications in patients receiving reserpine therapy. They showed that depletion of platelet serotonin caused no significant alteration of the bleeding time, blood coagulation mechanisms or capillary fragility. It would appear that there is no relationship between reserpine administration and peptic ulcer as far as serotonin is concerned. Therefore, the occurrence of peptic ulcer in patients receiving Rauwolfia alkaloids is in all probability related to the increase in gastric secretory activity.

In our hospital there have been 42 cases of perforation or hemorrhage from duodenal ulcer over a one and one-half year period; three—and probably five—of these cases were associated with or thought to be secondary to the administration of *Rauwolfia serpentina* (11.9%). In this same group there were five others thought to be secondary to ACTH or cortisone, and one to phenylbutazone (Butazolidin). In this study there were four white males and one white female, all over the age of 50. All had been taking oral and/or parenteral *Rauwolfia serpentina* for varying periods of time. Four gave ulcer histories, one of which was not uncovered on the initial work-up. The time between onset of therapy and the occurrence of ulcer complications varied from four days to over one year. All lesions were in the duodenum except possibly case 4, which was equivocal (table 1).

The important question to be answered is whether the administration of *Rauwolfia serpentina* associated with the occurrence of these ulcer complications was coincidental or causal. We are inclined to both a significant and a causal relationship, for the reasons given. The figures reported in

this series with *Rauwolfia serpentina,* as well as with ACTH, cortisone and phenylbutazone, are alarmingly high and should make us critical of ourselves. Every patient seen on either an in-patient or an out-patient basis deserves a complete history and physical examination, not slighting the review of systems and history of drug intake. If for some physical or mental reason (shock, coma, alcoholism, schizophrenia, etc.) the patient is unable to give an adequate account of his illness, it should be obtained as quickly and completely as possible from some person who knows the patient's history. Any failure or laxity on this part of the job may cost the patient's life, as it might have in case 4.

From our experience it would seem wise to use caution when *Rauwolfia serpentina* is employed in patients. Care must be taken in evaluating these patients as to past or present gastrointestinal symptoms. No patient, whether hypertensive, psychoneurotic or psychotic, who gives a history which suggests peptic ulcer should be given these agents. If no contrain-

TABLE 1

Case	I	II	III	IV	V
Age	70	54	53	54	82
Race and sex	WM	WM	WM	WM	WF
Ulcer history	No	Yes	Yes	Yes	Yes
Location	Duodenum	Duodenum	Duodenum	Duodenum or Prepyloric	Duodenum
Drug	Reserpine	Reserpine	Alkaloid ? type	Raudixin	Eskaserp
Route (O or P)	O	O & P	O	O	O
Complication	Perforation	Hemorrhage	Perforation	Hemorrhage	Hemorrhage
Time from drug intake until hemorrhage or perforation	4 days	13 days	6 months	over 1 year	7 days

dications exist, however, they may be employed, always keeping in mind the complications which might arise. Since *Rauwolfia serpentina* causes a fairly sudden and sustained rise in gastric acidity, this action must be buffered by meals and/or antacids, or, preferably, by both. If vague or specific upper gastrointestinal symptoms occur during the course of therapy, the agent should be stopped and the patient evaluated clinically and, if possible, by x-ray examination.

From the foregoing cases, discussion and literature review, it seems logical and practical to assume that there is a close, if not causal, relationship between the administration of *Rauwolfia serpentina* and the occurrence, recurrence and complications of duodenal ulcer.

SUMMARY AND CONCLUSIONS

1. Five proved cases of complicated duodenal ulcer, diagnosed clinically, by x-ray or by surgery, were presented. All of these patients were taking

Rauwolfia serpentina for hypertension when the complications developed. This was thought to represent a causal relationship. These cases accounted for approximately 12% of all the perforations and hemorrhages from duodenal ulcer seen at our 250-bed general hospital over a one and one-half year period. There were four white males and one white female in this study, all over the age of 50; four gave a fairly definite history of peptic ulcer.

2. *Rauwolfia serpentina* should not be used in patients who have peptic ulcer.

3. If these agents are employed, for whatever reason, the potential rise in gastric acidity should be buffered with antacids or between-meal feedings prophylactically. Anticholinergic drugs are probably of little value.

4. If vague or specific upper gastrointestinal symptoms develop during the course of therapy, the agent should be stopped and the patient evaluated clinically and, if possible, by x-ray examination.

5. In cases when an adequate history is unobtainable, or in patients who cannot communicate their feelings, another antihypertensive or tranquilizer, if indicated, should be employed.

6. The key to correct diagnosis and good therapy rests for the most part in a well documented history, never slighting the review of systems and history of drug intake.

7. We feel that mild, labile essential hypertension is best treated with phenobarbital sedation, low salt diet, and weight reduction if the patient is overweight.

8. Peptic ulcer occurrence, recurrence and complications associated with the administration of *Rauwolfia serpentina* probably contribute another to the evergrowing list of "diseases of medical progress."

Summario in Interlingua

Es presentate cinque casos de provate complicate ulcere peptic duodenal, diagnosticate clinicamente, roentgenographicamente, o chirurgicamente. Omne iste patientes recipeva *Rauwolfia serpentina* o su alcaloides in administrationes oral e/o parenteral como tractamento de hypertension quando iste complicationes se declarava. Viste que le agentes in question causa un augmento de aciditate gastric, le relation es interpretate como causal plus tosto que coincidental. Le cinque casos del presente reporto representava circa 12% de omne le perforationes e homorrhagias de peptic ulcere duodenal vidite durante un anno e medie a nostre hospital general con su capacitate de 250 lectos. Quatro del patientes esseva masculos de racia blanc. Un esseva un femina de racia blanc. Omne le patientes habeva plus que 50 annos de etate. Quatro presentava un historia satis definite de ulcere peptic. Perforation occurreva in duo, hemorrhagia in tres. Un patiente moriva. Le intervallo inter le administration del droga e le declaration del complicationes esseva quatro dies, septe dies, 13 dies, sex menses, e plus que un anno.

Le datos permitte le formulation de plure conclusiones: (1) Il es probabile que *R. serpentina* e su derivatos es contraindicate in patientes con ulcere peptic o un historia de tal. (2) Quando iste agentes es usate, le augmento potential del aciditate gastric deberea esser tamponate con antacidos o alimentation inter le repastos regular. (3) Si vage o specific symptomas supero-gastrointestinal se disveloppa in le

curso del therapia, le medication debe esser arrestate, e un evalutation clinic e, si possibile, roentgenologic debe esser interprendite. (4) Omne patiente individual merita un historia adequate in que un revista del systemas e un historia del ingestion de drogas non debe esser negligite. (5) In casos in que un adequate historia non es obtenibile, un altere agente antihypertensive o tranquillisante, si indicate, debe esser usate. (6) Le uso promiscue de iste agentes in hypertension e statos de tension debe esser condemnate.

Super le base del casos hic describite e de un revista del litteratura, il pote esser asserite que il existe un intime e forsan causal relation inter le administration de *R. serpentina* o su derivatos e le occurrentia, le recurrentia, e le complicationes de peptic ulcere duodenal.

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A SCREENING METHOD FOR THE EVALUATION OF URINARY TRACT INFECTIONS IN FEMALE PATIENTS WITHOUT CATHETERIZATION * †

By BURIS R. BOSHELL, M.D.,‡ *Boston, Massachusetts,* and JAY P. SANFORD, M.D.,§ *Dallas, Texas*

EARLY, accurate diagnosis and adequate therapy are important in the management of urinary tract infections, [1, 2, 3, 4] which often progress to chronic pyelonephritis, with the development of uremia or hypertension in the later stages. Minor symptoms or minimal pyuria is often the only clinical finding in the presence of serious infection.[1, 2, 3] Bacteriologic evaluation of patients with seemingly insignificant symptoms is thus important, if it can be done without hazard. The commonly accepted technic for obtaining urine for culture from female patients involves the use of bladder catheterization. It has been widely appreciated that catheterization per se carries with it the hazard of introducing organisms into the bladder which are capable of producing urinary tract infection.[1, 5] The risk of introducing infection must be weighed against the possibility of overlooking relatively silent infections.

In evaluation of the report on any urine culture, the possibility of contaminants must be considered. The use of quantitative bacterial counts is of great help in the evaluation of catheterized urine specimens.[1, 5-7] In catheterized specimens of urine obtained under careful observation, more than 10,000 bacterial colonies per milliliter of urine are usually found with infection, while contaminants rarely exceed concentrations of 1,000 colonies per milliliter of urine.[6]

If reliable, extension of this method to the study of clean-voided urine specimens obtained from female patients seemed to offer a safe method of screening patients with minor symptoms suggestive of infection. This

* Received for publication March 27, 1957.

From the Department of Medicine, Peter Bent Brigham Hospital, and Harvard Medical School, Boston, Massachusetts.

† Supported by the Fund for Research in Bacteriology of the Peter Bent Brigham Hospital.

‡ Research Fellow in Medicine, Harvard Medical School, and Junior Associate in Medicine, Peter Bent Brigham Hospital.

Recipient of a Fellowship from The American College of Physicians, Philadelphia, Pennsylvania.

§ Research Fellow in Medicine, Harvard Medical School, and Assistant in Medicine, Peter Bent Brigham Hospital.

Work completed during the tenure of a post-doctorate Fellowship of the National Institutes of Health, Bethesda, Maryland.

Requests for reprints should be addressed to Buris R. Boshell, M.D., Peter Bent Brigham Hospital, 721 Huntington Avenue, Boston 15, Massachusetts.

study is an evaluation of the usefulness of clean-voided urine specimens obtained from female patients for bacteriologic studies.

Methods and Materials

1. Initial subjects for this study were 46 patients admitted to a semi-private medical ward. Only two of these patients had admission diagnoses suggestive of urinary tract infections, i.e., trigonitis and cystitis.

2. A second group of subjects were studied on a general medical female ward service. This group consisted of 21 patients from whom both clean-voided and catheterized urine specimens were collected on the same day.

3. Clean-voided urine specimens:

A. Collection technic: A clean-voided specimen was obtained by having the patient sit in a Sitz chair which had been previously filled with a green soap solution. Patients were instructed to wash the labia, perineum and inguinal regions carefully for about five minutes. The urethral orifice and surrounding areas were then scrubbed with Zephiran sponges either by the nurse or by the patient. Following this, the patient moved to a commode or stool chair and was instructed to hold the labia apart and void. The first portion of each sample was discarded. The second portion was collected in two sterile tubes, one of which was used for routine examination and the other for culture. All specimens were cultured within 60 minutes after having been obtained. The second group of patients were instructed to stop voiding as soon as the clean-voided specimen was obtained. Each patient was then immediately catheterized and a specimen was obtained for culture.

B. Routine examination: Each specimen was tested for pH, specific gravity, protein, reducing substances, and after centrifugation the sediment was studied microscopically.

C. Bacteriologic examination: Samples of urine were centrifuged, then the sediment was stained with methylene blue and examined for bacteria. The number of bacteria per milliliter of urine was determined by thoroughly mixing a measured aliquot of the urine which had not been centrifuged with tryptic digest agar in a Petri dish. When the agar had solidified the culture was incubated for 18 hours at 37° C., then the individual bacterial colonies on the plate were counted ("pour-plate"). To facilitate counting the colonies, the size of the original inoculum of urine was varied from 0.001 to 1.0 ml., depending upon the number of bacteria noted in the stained sediment; however, all cultures were corrected to the number of bacterial colonies per 1.0 ml. of urine. Standard biochemical fermentation reactions and cultural characteristics were used for the identification of all bacterial strains isolated.

4. Catheterized urine specimens: Catheterized specimens of urine were obtained from those patients in the first group whose clean-voided specimens were found to contain more than 1,600 colonies per milliliter, and from

TABLE 1

43 Clean-Voided Cultures in 40 Female Patients (Group I-A)

Negative	14
1–100 organisms/ml.	13
100–500 organisms/ml.	10
500–1,000 organisms/ml.	4
1,000–1,600 organisms/ml.	2
Total	43

each of the second group. Laboratory studies as described above were carried out on these specimens.

RESULTS

1. *Group I.* The incidence of the varying degree of bacteriuria in clean-voided specimens was plotted to ascertain whether there would be two roughly separated groups, i.e., contaminated urines and infected urines. There appeared to be two rather distinct groups: one in which the degree of bacteriuria was 1,600 colonies per milliliter or less (Group IA, table 1), and another, much smaller group in which the degree of bacteriuria was 6,000 colonies per milliliter or greater (Group IB, table 2).

2. *Group IA.* Group IA consisted of 40 patients. The clean-voided urines contained no bacteria in 14 of these, and 0 to 1,600 organisms per milliliter in 26.

3. *Group IB.* Group IB consisted of six patients who had 6,000 or more organisms per milliliter on clean-voided cultures. Each was checked with a catheterized specimen, and the comparison is shown in table 2.

4. *Group II.* This group of 21 patients was studied to determine whether the results obtained in the clean-voided specimens could be confirmed by a catheterized specimen obtained immediately after each clean-voided specimen. The results are shown in table 3.

Catheterized specimens on three of the 500 to 1,600 organism/ml. group were negative. These results are consistent with those of Sanford et al.,[6] Kass [5] and Guze and Beeson,[7] i.e., as many as 1,000 organisms/ml. can occur due to contamination, whereas most infected urines contain 10,000 or more organisms per milliliter. This is especially significant when the culture is taken as the first morning urine, as most of these were. Urine is an excellent culture medium, thus bacteria present in the urinary tract will have multi-

TABLE 2

Comparison of Clean-Voided and Catheterized Specimens from Seven Female Patients with Urinary Tract Infection (Group I-B)

Organisms/ml. of urine	
Clean-Voided	Catheterized
6,000	640
320,000	24,000
>10,000	>10,000
>10,000	>10,000
>10,000	>10,000
>10,000	>10,000

plied into maximal concentration in the bladder urine overnight and will be present in sufficient quantities to be seen on stained slides and to give counts of greater than 10,000/ml. on pour plating. The effectiveness of the cleansing procedure was demonstrated by collecting several specimens for culture without prior cleansing. All such urines contained more than 10,000 organisms per milliliter. The majority of these positive cultures were *Staphylococcus albus,* alone or mixed. This fact was also noted by Sanford et al.[6] This is in marked contrast to the organisms in Group II, in which the majority were either *Escherichia coli, Aerobacter aerogenes,* or Proteus.

TABLE 3

Comparison of Clean-Voided and Catheterized Specimens from 21 Female Patients (Group II)

	Organisms/ml. of urine	
	Clean-Voided	Catheterized
1.	>10,000	130,000
2.	28	0
3.	90	0
4.	70	4
5.	>10,000	>10,000
6.	80	0
7.	150	0
8.	750	0
9.	360	0
10.	900	0
11.	>10,000	>10,000
12.	280	50
13.	0	0
14.	>10,000	>10,000
15.	0	0
16.	25	0
17.	0	0
18.	250	18
19.	600	0
20.	5	0
21.	>10,000	>10,000

All organisms were identified and were found to be identical in clean-voided and catheterized specimens.

SUMMARY

Clean-voided specimens have long been used for cultures from male patients, but catheterization has usually been necessary to obtain adequate cultures from the female. This presented the paradox of not infrequently instigating an infection in the process of trying to establish a diagnosis. Because of this situation, a clean-voided technic was devised and evaluated for use in the female.

Sanford et al.[6] and Kass [5] have previously demonstrated that as many as 1,000 organisms per milliliter can occur as contaminants in a catheterized urine specimen, whereas in the case of a urinary tract infection at least 10,000 organisms per milliliter are demonstrable if the first morning specimen is taken for culture. The same criteria were applied in the evaluation of the clean-voided technic.

The procedure for collection of the specimen consisted of having the patient do a thorough cleansing of the periurethral area in a Sitz chair filled with green soap solution followed by scrubbing with Zephiran pads. The patient then voided, holding the labia apart, and a midstream specimen was caught for culture.

Sixty-seven patients were studied. The first group consisted of 46 patients, of whom six were found to have in the vicinity of 10,000 or more organisms per milliliter. The other 40 patients had 0 to 1,600 organisms per milliliter. A follow-up catheterization of a few of these 40 patients failed to reveal significant bacteriuria.

Twenty-one patients had both clean-voided and catheterized specimens taken at the same time. Five of this group had more than 10,000 organisms per milliliter on clean-voided culture, and in each case the catheterized specimen confirmed this. The other 16 patients had 900 or fewer organisms per milliliter in both clean-voided and catheterized cultures.

It is concluded that quantitative bacterial counts are necessary for the proper evaluation of any urine culture, and that if this procedure is available in the bacteriologic laboratory a properly collected, clean-voided specimen is adequate for culture in both the male and the female. The major advantage of this procedure is that it avoids the hazard of catheterization, thereby allowing one to make a positive diagnosis without the risk of introducing bacteria into the bladder.

This procedure is simple and may be used in the home, office or hospital. It is not applicable to the uncoöperative patient.

Acknowledgments

The authors wish to express their appreciation to Anna M. Free, Frances Mao, Elizabeth Reddy and Frances Wheelright for their able technical assistance.

Summario in Interlingua

Esseva disveloppate un methodo pro le collection de specimens de urina non-contaminate ab patientes feminin. Le specimens, obtenite sin catheterisation, es apte pro objectivos de culturation. Le patiente se absterge systematicamente in le area periurethral in un banio-sede que es plenate de un solution de sapon verde. Isto es sequite per un vigorose frictionation con spongias a Zephyran. Postea le patiente se evacua, tenente le labios distaccate, e un specimen es obtenite al centro del fluxo.

Le methodo esseva usate in le studio de duo gruppos de patientes. Le prime consisteva de 46 non-seligite patientes in un semi-private section medical. Sex de iste patientes habeva in le vicinitate de 10.000 organismos per millilitro. Le remanente 40 patientes habeva inter 0 e 1.600 organismos per millilitro. Plures inter le 40 patientes esseva restudiate per catheterisation, e isto non revelava grados significative de bacteriuria.

In 21 patientes specimens de urina esseva prendite simultaneemente per le methodos (1) a evacuation non-contaminate e (2) a catheterisation. In cinque individuos de iste gruppo, plus que 10.000 organismos per millilitro esseva trovate in le specimen a evacuation non-contaminate, e in omne iste casos le specimen obtenite per catheterisation confirmava le resultato. Le remanente 16 patientes habeva 900 o minus organismos per millilitro in ambe typos de specimen.

Sanford [6] e Kass [5] ha previemente demonstrate que usque a 1.000 organismos per millilitro occurre como contaminantes in un specimen de urina obtenite per catheterisation, durante que specimens de urina inficite contine al minus 10.000 organismos per millilitro, providite que le prime specimen matinal es usate pro le cultura. Per applicar le mesme criterios a specimens obtenite per le methodo a evacuation non-contaminate on arriva al conclusion que iste technica—si executate secundo le supra-presentate description—es apte al obtention de specimens pro objectivos de culturation.

Le principal avantage del methodo es que illo evita le hasardos del catheterisation. Illo permitte le establimento de un diagnose positive sin que on curre le risco de introducer bacterios in le vesica. In plus, le technica es simple e pote esser usate al domicilio del patiente, al sala de consulta del medico, o al hospital. Evidentemente, illo non pote esser applicate sin le cooperation del patiente.

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A DISCUSSION OF THYROID PARAMETERS *

By RICHARD P. SPENCER, Lieutenant (MC) U.S.N.R., E. RICHARD KING, Captain (MC) U.S.N., *Bethesda, Maryland,* CHARLES R. HENKELMANN, Lieutenant (MC) U.S.N.R., *Bakersfield, California* and THEODORE G. BALBUS, Lieutenant (MC) U.S.N.R., *Oakland, California*

A USEFUL concept in orienting our thinking about the thyroid is to consider its parameters. The term parameter has gained use in medicine to indicate an arbitrary test for quantitating some aspect of metabolism. For instance, to study the thyroid we can employ such determinations as the basal metabolic rate. But do these arbitrary procedures measure thyroid activity and, if so, can such activity be quantitated? This paper is concerned with an evaluation of parameters proposed for studying the thyroid gland.

To be valid, a test of thyroid activity must fulfill two requirements. First, it should measure a function that is truly dependent upon the gland, and not influenced by other factors. Second, the measurement must correlate quantitatively with the final clinical diagnosis. Before proceeding, we must realize that any test will have a range of values within the "normal limits of variation." There is often an overlap between groups, and no single study should be relied upon to separate definitively all classes of thyroid activity.

Thyroid physiology is intimately linked to iodine, and there is often difficulty in discussing one without the other. Indeed, some of the so-called "thyroid parameters" may actually represent phases of iodine metabolism that lie outside of endocrine control. The approximate extent of our knowledge of body iodine handling is indicated schematically in figure 1. It should be apparent that multiple sites, enzymes and excretory pathways are involved. Hence, no one test can ever be expected to define the system completely.

STUDIES OF END ORGAN RESPONSE

The striking pictures of cretinism and myxedema impressed early investigators, but their hypometabolic nature did not become clear until the investigations of Magnus-Levy.[1] In the following years, evaluation of the metabolic status in a resting condition proved to be of value in diagnosing either under- or overactivity of the thyroid. However, this "basal metabolic

* Received for publication February 8, 1957.

From the Radioisotope Laboratory, U. S. Naval Hospital, and the Radioisotope School, U. S. Naval Medical School, National Naval Medical Center, Bethesda, Maryland. The opinions expressed herein are those of the authors, and do not necessarily reflect the views of the Medical Department, or the Naval Service at large.

Presented in part at the Maryland-Washington, D. C., District Meeting of The American College of Physicians, January 12, 1957.

Requests for reprints should be addressed to Radioisotope Laboratory, U. S. Naval Hospital, Bethesda, Maryland.

rate" has been much criticized in recent years. A patient traveling to the laboratory through heavy traffic is seldom in a basal condition. In addition, febrile states, cardiac disorders and a host of other diseases cause abnormal test results.

The elevation of serum cholesterol that may occur in hypothyroidism [2] has been claimed to be of quantitative diagnostic aid. However, there are other conditions which elevate blood lipids. As a further complication, certain cases of hypothyroidism have no accompanying elevation of serum cholesterol.

Despite these limitations, the basal metabolic rate and the concentration of blood cholesterol are unique in one respect. They are the only quantita-

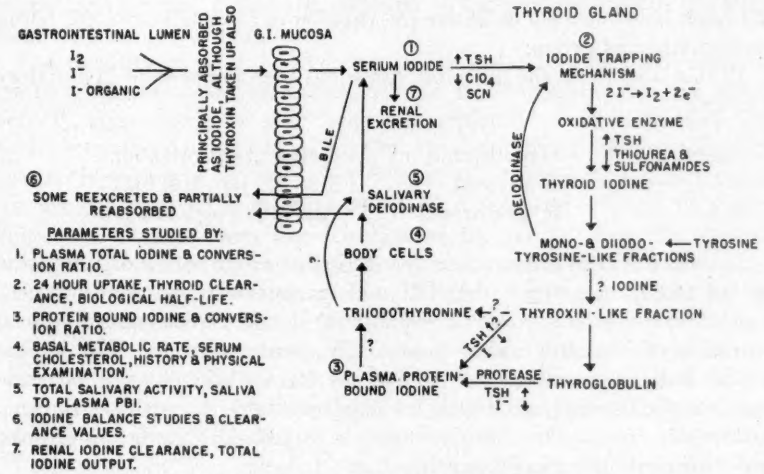

FIG. 1. Scheme of body iodine metabolism.

tive studies available as to the effect of the thyroid hormone on its end organ, the somatic cells. All other measurements of "thyroid function" depend primarily upon the handling of iodine by the gland.

CHEMICAL PBI AND EXCRETION OF IODINE

The thyroid is obviously not in propinquity to all body tissues. The blood stream serves as a channel for conveying thyroid end product(s) to other areas. The assay of these circulating iodine fractions has proved a fertile field.

It was noted relatively early in such investigations that a major portion of blood iodine was bound to protein. The total amount of iodine in the blood is quite small, and unless one is blessed with a conscientious and scrupulous laboratory, determinations of iodine bound to protein should be avoided. A variety of technics are now available for estimating the iodine-

protein fraction, and this may be expressed as: protein-bound iodine (PBI), serum precipitable iodine (SPI), or butanol-extractable iodine (BEI).

Hyperthyroid patients were found to have elevated quantities of iodine linked to plasma proteins. Even though the nature of the thyroid hormone was uncertain, it seemed reasonable that the PBI gave an approximation of the circulating active principle. Some difficulties are encountered with the PBI. If the test truly measured the thyroid hormone, a PBI of zero would occur following total thyroidectomy. This does not take place, and rarely can we find a PBI below 0.5 μg. per 100 ml. of plasma. Tri-iodothyronine sufficient to cause signs and symptoms of hyperthyroidism may not elevate the PBI.[8] Further, the PBI does not differentiate between possible alterations in the type(s) of thyroid hormone produced. In our experience, the PBI often fails to supply definitive information in cases falling in the borderline hyperthyroid group.

In this laboratory, the following range has been found valid in a majority of cases.

Chemical PBI:	Hypothyroid	Below 3 μg./100 ml.
	Euthyroid	3 to 7.5 μg./100 ml.
	Hyperthyroid	Above 7.5 μg./100 ml.

If there has been access to exogenous iodine (thyroxin, inorganic iodine, various radiopaque dyes), the PBI will be spuriously elevated. When it is above 7, the serum inorganic iodine level should be determined. A concentration of inorganic iodine numerically greater than the PBI indicates possible iodine contamination. Iodine interference with thyroid parameters is apparently not easily produced, but requires sizable quantities of the anion. Particularly troublesome are dyes used in gall-bladder studies, and opaque media injected during myelography.

Non protein-bound iodine in the blood stream can be filtered by the kidney. The euthyroid person excretes about 150 μg. of iodine in the urine per day. Although there is increased iodine in the blood of thyrotoxic patients, much of it is protein-bound and nonfilterable. Hence, individuals with hyperthyroidism excrete less iodine in their urine. Clearance of iodine by the kidney could be calculated before the availability of radioactive iodine. However, the determination of iodine in urine is chemically difficult, and a 24-hour specimen is necessary. The technic never enjoyed popularity because of these drawbacks.

It can be seen that quantitation of thyroid function prior to the availability of isotopes was limited, and consisted of four procedures:

1. Basal metabolic rate.
2. Serum cholesterol.
3. Protein-bound iodine.
4. Urine iodine excretion.

Diagnostic I^{131} Studies

In the experience of this laboratory, three parameters which can be evaluated by means of radioactive iodine have often correlated with the patient's thyroid status. All three are routinely performed on individuals referred here for diagnostic evaluation. These are the 24-hour I^{131} uptake, the radioiodine conversion ratio, and the saliva-PBI^{131} ratio.

1. *24-Hour I^{131} Uptake.* The most outstanding feature of the thyroid gland is its ability to concentrate iodine. Within the gland, iodine may be at a concentration 50 to several hundred times that of the blood stream. Maintenance of this gradient is to a certain extent not related to hormone production, and depends upon a distinct enzyme system. It cannot be sufficiently stressed that iodine accumulation is the primary step in the metabolism of this anion by the thyroid.

The quantity of radioactivity required for the test depends upon the sensitivity of the detection apparatus. If blood studies are run simultaneously, larger amounts of I^{131} must be employed. Geiger counters with low efficiency require more of a dose than do sensitive scintillation detectors.

After ingestion of carrier-free I^{131} in distilled water, the accumulation of radioactive material in the thyroid can be determined. With the patient sitting at a distance from the detection probe, activity over the neck is counted, and corrected for background. A vast number of variations on this basic procedure have been proposed. However, in their complexity the proposals do not take account of the fact that radioiodine in the neck depends upon the dual factors of accumulation and release. A mathematical exposition of this relationship has been presented by Brownell [4] and others. Because of the dependence of the uptake on more than one variable, it should be viewed as a dynamic rather than a static figure.

Various laboratories calculate the amount of I^{131} in the thyroid at one, three, four, six, or 48 hours after the dose is administered. For the sake of convenience, the 24-hour figure is most commonly used. This is also physiologically sound, since one day following radioiodine ingestion the anion has had ample opportunity to be cleared from the blood stream. In a series of cases from this laboratory, the following results have been obtained:

24-Hour Uptake in Per Cent of Administered Dose

Hypothyroid	Under 15%
Euthyroid	15 to 45%
Hyperthyroid	Greater than 45%

The 24-hour uptake agreed with the final clinical diagnosis in 85% of a consecutive series of 468 determinations. As with other procedures, there is some overlap of values between the various degrees of thyroid function. Values at variance with the clinical diagnosis may also be produced by an excess of exogenous iodine.

It is also possible that the ability to accumulate iodine may be intact while hormone synthesis is impaired. We have been studying a 36 year old woman with a large diffuse goiter and myxedematous features. These findings, as well as a chemical PBI below 3 mg./100 ml., indicated hypothyroidism. Yet there was a 55% uptake of radioiodine, and the value did not fall following the ingestion of large quantities of exogenous tri-iodothyronine.

Radioiodine Conversion Ratio. Iodine in the blood stream exists in both inorganic and protein-bound forms. If radioiodine is given, it can be detected in both blood fractions. Hence the ratio: $\frac{\text{protein-bound } I^{131} \times 100}{\text{total } I^{131} \text{ in blood}}$ can be calculated. This has been proposed as an index of thyroid function.

The procedure is mechanically simple to perform. Two milliliters of serum are counted in a well-type scintillation counter. The serum is then run through an anion exchange resin (such as Amberlite-IRA-400 Cl).[5] About 95% of inorganic iodine is held by the resin column, while protein-bound iodine passes through (and can be counted). The amount of iodine converted to the protein-bound form increases with time, leveling off at about 24 hours.

Several other methods for calculating the conversion ratio are available; they depend primarily upon precipitating the protein fraction, and then counting the precipitate. This laboratory performed four different methods for the conversion ratio, and found all gave reproducible results. Because of ease of handling, the ion exchange method has been our procedure of choice.

What is the significance of the conversion ratio? Is it truly a measure of thyroid activity? In the experience of this laboratory, there has been no correlation between low values of the ratio and the patient's clinical status. Unexpectedly, the test was of assistance in the diagnosis of hyperthyroidism. The conversion ratio correlated more often with the diagnosis of thyroid overactivity than did any other procedure. Why should this be so? A definitive answer cannot be given. In the hyperthyroid gland, there may be an avid mechanism for converting inorganic iodine to a bound form.

At present, we are using the following values in interpreting the conversion ratio.

Conversion Ratio: Hypothyroid below 45%
Euthyroid below 45%
Hyperthyroid above 45%

The quantity of radioiodine present in the blood stream 24 hours after a tracer dose has been proposed as a test of thyroid activity ("per cent dose per liter"). Since this figure is influenced by the blood volume and other factors that may have little relation to the thyroid, it often proves of little value.

3. *Saliva-PBI^{131} Ratio.* Following administration of iodine by either oral or parenteral routes, small amounts of I^{131} can be detected in saliva. It

has been shown that iodine secretion is an active process performed by the salivary glands. Hyperthyroid patients, with an increased rate of turnover and elevated blood PBI, apparently retain iodine more avidly than do euthyroid individuals. Conversely, the hypothyroid patient, with little use for the anion, excretes more iodine in the saliva.

To estimate the extent of salivary iodine transport, the saliva-PBI^{131} ratio has been proposed: $\frac{\text{radioactivity of 2 ml. saliva}}{\text{radioactivity of PBI in 2 ml. serum}}$. There appears to be little relationship between serum inorganic iodine and the quantity of the anion in saliva. However, a more definite correlation exists between the ratio of protein-bound I^{131} to salivary I^{131}. In our experience, the iodine of saliva is entirely inorganic. It may arise as the result of a salivary de-iodinating system, which removes iodine from one or more blood protein-iodine combinations. Why this function should be depressed in the hypothyroid subject is not known.

Free-flowing saliva is collected in a waxed cup, and 2 ml. are placed in a well-type scintillation counter. The PBI^{131} is determined by use of anion exchange resin (as in the conversion ratio), utilizing 2 ml. of serum. The following values are used in this laboratory:

Saliva-PBI^{131} Ratio: Hypothyroid over 300
Euthyroid 50–299
Hyperthyroid under 50

Lack of agreement between the saliva-PBI^{131} ratio and the clinical diagnosis may be due in some cases to failure of the salivary apparatus to correlate exactly with thyroid function. In only 70% of a series of 377 determinations did the ratio tally with the final clinical impressions. However, when hypothyroidism was present, the saliva-PBI^{131} ratio proved more reliable (80%) than did the 24-hour uptake, chemical PBI, or conversion ratio.

This difference between the reliability of tests in the various thyroid states brings up interesting questions. The multitude of thyroid functions are apparently not inseparably linked, and one may vary without the others. If only one test were performed on an individual, to evaluate the status of the thyroid, on the basis of the experience of this laboratory the following would be performed:

Clinical State	Most Reliable Test
Hypothyroidism	Saliva-PBI^{131} ratio
Euthyroidism	24 hour I^{131} uptake
Hyperthyroidism	Conversion ratio

It should be repeated, however, that there is often an overlap between groups, as measured by any test. Thus a series of studies is always indicated.

Other Radioiodine Parameters

Urinary Excretion: Urine was extensively studied during initial experiments on the distribution of I^{131}. Thyrotoxic patients excreted from zero to 50% of the administered dose in the first 24-hour period. However, there was a considerable overlap, in the 20 to 40% range, between euthyroid and normal groups. Routine determinations of the 24-hour I^{131} excretion is thus not a useful procedure. There are two very specific indications for the determination of this value.

1. If an ectopic location of thyroid tissue is suspected, a 24-hour urine collection is indicated. The quantity of radioiodine in the neck and in urine should equal about 90% of the administered activity. If a significantly smaller amount is detected, search can be made for ectopic tissue which concentrates iodine.

2. Isotope treatment of thyroid carcinoma and its metastases is feasible only in tumors which take up radioiodine. Once the thyroid gland has been removed, the amount localized by the tumor can be determined by subtracting the quantity in the urine from the ingested dose.

Since the thyroid removes iodine from the blood stream, it is effectively acting as a filter, to "clear" the anion. Hence, the concept of "clearance" as applied to renal physiology can be adapted to thyroid evaluation. The technic involves the injection of sterile NaI^{131} (tagged sodium iodide) and the determination of radioiodine in the neck region and in blood. The relationship of thyroid I^{131} blood-I^{131} is calculated. Average figures for the volume of blood cleared of radioiodine are:

Thyroid I^{131} Clearance (in ml./min.):

Hypothyroid	2
Euthyroid	17
Hyperthyroid	210

The range of values is large, and there is some overlap between groups. Because of mechanical complexities in performing the test, it has not been adapted to routine use. On theoretic grounds, this may be one of the most valid thyroid studies, since it measures the ability of the gland to concentrate iodine. The bile also "clears" iodine, and some of the cleared material is lost in the stool. Myant [6] has quantitatively studied biliary I^{131} clearance in human patients who had a T-tube in the bile duct.

Binding of tri-iodothyronine to tissues can be demonstrated. Freedberg's group has studied the uptake of tri-iodothyronine-I^{131} by red blood cells. The uptake is increased in hyperthyroidism and decreased during thyroid underactivity. The possibility is thus present that the test may have diagnostic value, although the mechanism of its action has not been elucidated.

Thyroid Stimulation

Thyroid underactivity may follow either from intrinsic disease of the gland or from lack of pituitary thyroid-stimulating hormone (TSH). When a patient exhibits hypothyroid values for the I^{131} tests, 5 units of TSH can be administered intramuscularly, and the tests repeated 24 hours later.

Following TSH administration, cases of hypothyroidism secondary to pituitary disease exhibit an increased 24-hour I^{131} uptake. Instances of primary thyroid underactivity do not respond to the pituitary hormone. On the basis of such a facile explanation, it would appear that the results were "cut-and-dried." Such is not the case. Various degrees of "thyroid reserve" (ability to respond to demand) have been delineated. In addition, the conversion ratio and the saliva-PBI^{131} ratio may not correspond to values expected on the basis of the 24-hour I^{131} uptake. Hence, this seemingly simple procedure has opened still newer avenues for investigation.

Suppression Test

Greer [7] demonstrated that exogenous thyroxin depressed the normal thyroid gland. Werner and Spooner [8] adapted this to differentiate between normal thyroid activity and hyperthyroidism. The latter used tri-iodothyronine as the suppressing agent (25 μg. three times a day for eight days, a total of 600 μg.). A postsuppression value for the 24-hour I^{131} uptake of below 20% was considered to be indicative of the euthyroid state. Such a value usually provides good demarcation between the normal and the hyperthyroid groups. However, an occasional patient will have a postsuppression uptake value in the 21 to 30% range. To avoid making a diagnosis on such an intermediate value, we have routinely evaluated four parameters, before and after the suppression test. The results to be expected are tabulated below:

Thyroid Studies Following Tri-Iodothyronine

	24-Hour Uptake	Conversion Ratio	Saliva-PBI Ratio	Chemical PBI
Normal	Below 20%	Below 45%	Above 50	No change
Hyperthyroid	Above 20%	Above 45%	Below 50	No change

Summary

Quantitative evaluation of thyroid function prior to the availability of radioactive iodine was limited. Several parameters have been proposed for the estimation of I^{131} handling by the thyroid. These studies are discussed and their applicability is evaluated. The 24-hour uptake, radioiodine conversion ratio and the saliva-PBI^{131} ratio are most commonly employed. Such tests do not have the same validity over the entire spectrum of thyroid

dysfunction, and a critique is given of their use in clinical diagnosis. All thyroid functions are not inseparably linked, and one may vary without the others.

SUMMARIO IN INTERLINGUA

Numerose tests de character arbitrari ("parametros") ha essite proponite pro evalutar le glandula thyroide. Ante le advento de radioiodo, le investigationes possibile esseva illos del metabolismo basal, del cholesterol seral, del iodo ligate a proteina, e del excretion de iodo in le urina. Le prime duo de iste tests, ben que de valor non illimitate, continua esser le soles disponibile pro estimar le effecto de hormon thyroide super cellulas somatic. Omne le altere tests que ha essite proponite depende del capacitate del glandula de laborar con iodo. Per consequente illos non se concentra super le ultime effectos de hormon thyroide.

In le experientia de iste laboratorio, le plus utile del tests que usa iodo radioactive es determinationes del acceptation de I^{131} in 24 horas, del proportion del conversion de iodo radioactive, e del proportion de I^{131} in saliva a I^{131} ligate a proteina. Iste determinationes mesura differente aspectos del function thyroide e possede, possibilemente, differente grados de applicabilitate in differente situationes. Le determination del acceptation de I^{131} ha monstrate su plus grande valor in le delineation de individuos euthyroide; le determination del proportion de I^{131} in saliva a I^{131} ligate a proteina esseva le plus utile como detector de hypothyroidismo, e le proportion del conversion de iodo radioactive pareva monstrar le plus alte correlation con le diagnose de hyperthyroidismo. In conjunction con iste studios on pote servir se de stimulation thyroide quando le valores (in le tests) es multo basse. Suppression thyroide pote esser effectuate per medio de triiodothyronina quando le valores trovate es multo elevate. Le clearance de radioiodo per le thyroide es etiam un indice de valor, sed su mesuration es clinicamente difficile a effectuar. Le excretion urinari de iodo radioactive ha monstrate pauc valor discriminatori a causa del coincidentia partial del valores in un population euthyroide e in un population con disordines thyroide e a causa del difficultate de effectuar un collection quantitative de urina.

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MACROGLOBULINEMIA: REPORT OF TWO CASES*

By Harry Glenchur, M.D., Horace H. Zinneman, M.D., F.A.C.P., and David R. Briggs, Ph.D., *Minneapolis, Minnesota*

In 1944 Waldenström presented his paper on "Incipient Myelomatosis or 'Essential' Hyperglobulinemia with Fibrinogenopenia—A New Syndrome?" In it he described three patients with refractory anemia and bleeding tendency whose sera exhibited a very high viscosity. Waldenström speculated that a special globulin fraction was the cause of the increased viscosity, and by ultracentrifugation studies he was able to demonstrate that the sera of two of these patients contained macroglobulins with molecular weights of over 1,000,000.[1] Since then other reports have been published, mostly from Europe, of single cases or small series, with a similar clinical picture and the presence of macroglobulins in the serum.

Macroglobulinemia is a chronic disease characterized by a greatly increased erythrocyte sedimentation rate, elevated serum globulin fraction due to the presence of globulins of unusually high molecular weights, ill-defined systemic symptoms, and various hematologic and hemorrhagic manifestations.[2,3] It occurs most commonly in elderly males.[3]

The following case reports present two patients exhibiting the macroglobulinemic phenomenon, with necropsy findings in one. We believe these cases of sufficient interest to be added to those previously reported.

Case Reports

Case 1. At the first admission of a 61 year old white male clerk on April 9, 1956, a three-week history of rapidly progressive unsteadiness of gait, weakness, loss of energy and dyspnea on exertion was obtained. Lately he had also noted slight ankle edema and pruritus of the thighs. Previous treatment with liver and iron preparations had been ineffective. On the day of admission the patient had a syncopal episode while waiting in his private physician's office.

The past medical history disclosed that the patient had had "growing pains" during childhood. In 1914 the patient had had what appeared to be a subdiaphragmatic abscess on the right, with resultant pneumonia and empyema. For the last year the patient had noted progressive weakness and atrophy of the small muscles of the left hand.

Physical examination revealed a well developed, well nourished, pale white male. The vital signs were normal. Funduscopic examination revealed a moderate number of flame- and boat-shaped hemorrhages without exudates. A 1 cm. perforation of the nasal septum was present. The tongue was normal. The lung fields were clear to auscultation. The heart was not enlarged. There was normal sinus rhythm with

* Received for publication February 18, 1957.

From the Veterans Administration Hospital, Minneapolis, Minnesota, the Department of Medicine, University of Minnesota Medical School, and the Department of Biochemistry, Institute of Agriculture, University of Minnesota.

Requests for reprints should be addressed to Horace H. Zinneman, M.D., Veterans Administration Hospital, Minneapolis 17, Minnesota.

an occasional premature beat. Presystolic crescendo and rumbling protodiastolic murmurs (grade II) were heard at the apex. The liver edge was percussed several centimeters below the right costal margin. The spleen was palpable 6 cm. below the left costal margin. Bilateral atrophy of the interosseous muscles of the hands was noted, more marked on the left. Large, discrete nodes were felt in the axillary and epitrochlear areas, and small, shotty nodes could be palpated in the inguinal regions. There was decreased pain sensitivity along the ulnar distribution of the left hand.

The leukocyte count was 4,600/mm.^{3}, with 81% neutrophils, 16% lymphocytes, 2% monocytes and 1% eosinophils. The hemoglobin was 3.6 gm. per 100 ml.; hematocrit, 12.5%; red blood cell count, 940,000/mm.^{3}; red blood cell indices: MCV, 132 cu. micra; MCH, 37 micromicrograms; MCC, 29%; MCD, 8 micra; reticulocyte count, 3.6%. The clot retraction, red cell fragility, bleeding and clotting times and cuff test were normal. The modified Schilling test* revealed at 10 hours a plasma radioactivity of 19 counts per minute (normal, 17 to 54) and a urinary radioactivity of 9.0% (normal, 5 to 18%). The prothrombin time was 14.9 seconds, with

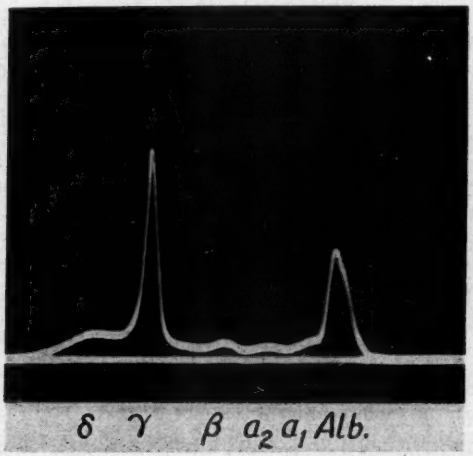

FIG. 1. Electrophoretic pattern (Tiselius) of the serum of the first patient, showing a slender homogeneous peak at the mobility of gamma globulin.

a control of 12.5 seconds. The prothrombin consumption was normal. A random stool specimen contained 414 E.U. per 100 gm. urobilinogen. A four-day stool collection contained 164 mg. of urobilinogen per day. The total serum proteins were 8.3 gm. per 100 ml., with 2.4 gm. albumin and 5.9 gm. globulin. Gastric analysis revealed no free acid after injection of histamine. The blood urea nitrogen was 22 mg. per 100 ml.; serum bilirubin, 0.2 mg. per 100 ml. direct and 1.5 mg. per 100 ml. total; zinc turbidity, 23.8 units, thymol turbidity, 18.6 units; serum cholesterol, 107 mg. per 100 ml. The serum alkaline phosphatase, calcium, phosphorus, bromsulfalein dye retention, Coombs' test, cephalin flocculation, three stool specimens for occult blood, the electrocardiogram and cold agglutinins were normal or negative. A "bedside" test for cold red blood cell macroagglutinins was positive.

X-ray films of the chest revealed the heart size at the upper limits of normal, normal hilar structures, blunted costophrenic angles and a deformity of the right

* Vitamin B_{12} (0.48 μg.) tagged with radioactive cobalt was given by mouth, followed in 24 hours by a flushing dose of 1,000 μg. of vitamin B_{12} intramuscularly.

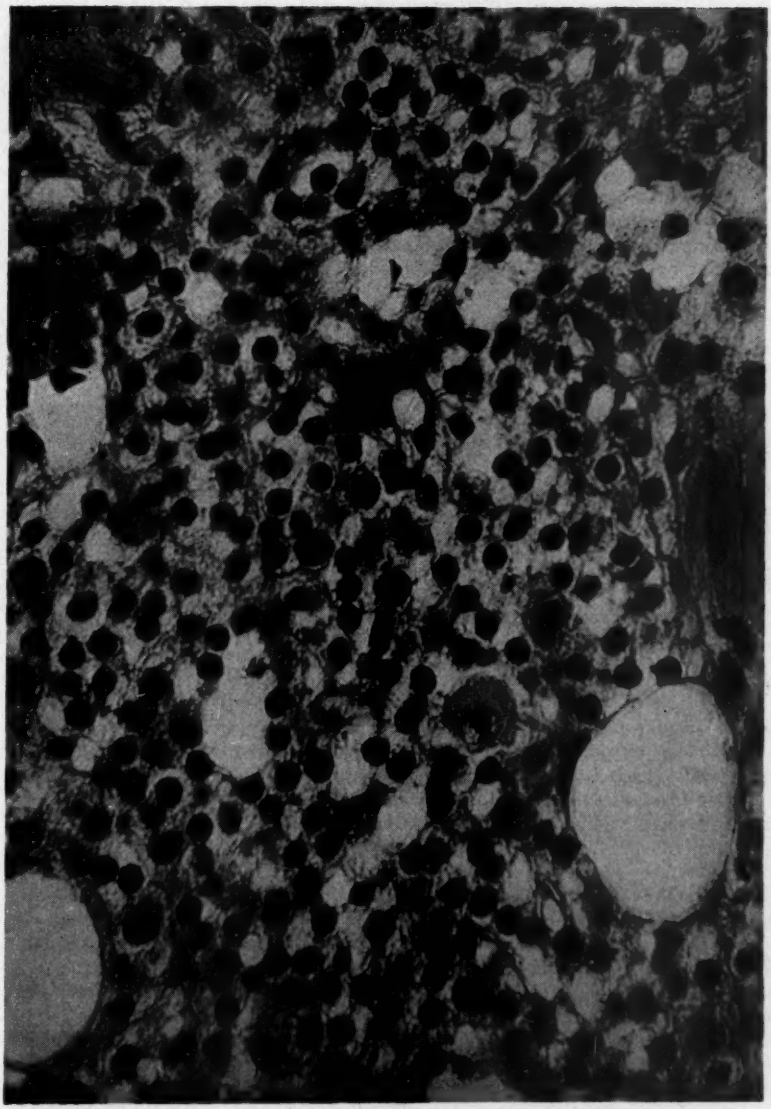

FIG. 2. Histologic section of the bone marrow of case 1, showing a general infiltration with mononuclear cells. Magnification 1:400.

seventh rib. Abdominal films confirmed the presence of hepatosplenomegaly. X-rays of the cervical spine showed posterior lipping in the midcervical region, with involvement of the neural canals; films of the thoracic and lumbar spine revealed mild degenerative changes. X-rays of the upper gastrointestinal tract, pelvis and skull were normal.

Serum electrophoresis revealed an albumin fraction of 2.4 gm.; alpha-1-globulin, 0.4 gm.; alpha-2-globulin, 0.4 gm.; beta globulin, 0.5 gm.; gamma globulin, 3.5 gm. per 100 ml. serum. The gamma globulin peak was high and narrow, denoting homogeneity of the fraction (figure 1).

After three unsuccessful attempts at bone marrow aspiration a trephine biopsy of the sternum was done. A bone marrow section showed that approximately 80 to 90% of the nucleated cells were uniformly small, mature lymphocytes with a thin rim of pale blue cytoplasm, lending a monotonous appearance to the field (figure 2). Plasma cells constituted 2.4% of the differential count. Most of these cells were normal; however, a few were larger, atypical forms, with fine to slightly clumped chromatin and single to multiple, medium to large nucleoli. Some of the young plasma cells appeared lymphoid. The myeloid and erythroid elements appeared normal but were reduced in number. A few normal megakaryocytes were seen. The

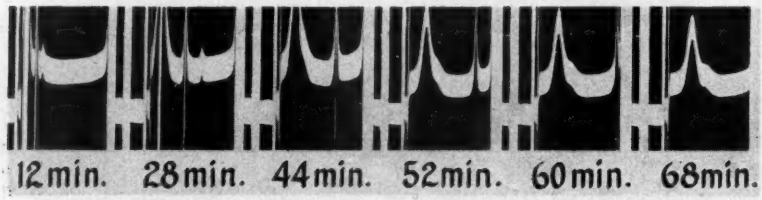

FIG. 3. Ultracentrifugation of the serum of case 1, showing the separation of the macroglobulin progressing at the indicated intervals.

increase in tissue mast cells was an outstanding feature of the bone marrow preparation.

Bence Jones protein was absent in the urine. Biopsy of a lymph node of the right axilla showed partial fatty replacement and fibrosis. The serum euglobulin test (Sia water test) was positive. Ultracentrifugation of the serum at 26° C. in a dilution of 1:4 with 0.5 M sodium chloride solution showed the presence of a large fraction of macroglobulin, with a sedimentation constant of 13.8 Svedberg units. In the same experiments the sedimentation constants of the albumin, gamma globulin and a second (normal) macroglobulin were 3.71, 5.60 and 20.3 Svedberg units, respectively (figure 3). One-half of the intravenously injected I^{131}-labeled gamma globulin disappeared in 5.9 days (normal, 9 to 11.5 days) (figure 4). The exchangeable pool of normal gamma globulin was calculated to be 37 gm.

Two successive injections of 0.5 ml. typhoid-paratyphoid vaccine provoked no agglutinins in the serum after three weeks. Serum influenza agglutinin titers were as follows: A 1:32, A′ 1:32, B 1:512.

The patient's hospital course was complicated by atrial fibrillation, which ceased with digitoxin. The patient was transfused to a hemoglobin level of 12.2 gm. per 100 ml. and started on a daily dose of 30 mg. prednisone. He was discharged to his home for five weeks. Upon return his blood studies were as follows: hemoglobin, 7 gm.%; leukocytes, 1850/mm.^{3}, with 46% neutrophils, 50% lymphocytes, 2% monocytes and 2% eosinophils. The sedimentation rate (Westergren) was 146 mm./hour. The total serum protein was 8.3 gm. per 100 ml., with 2.0 gm. albumin and 6.3 gm. globulin. The patient had not regained his full strength but felt well otherwise.

Physical examination now revealed one small hemorrhage in the right fundus, persistence of the cardiac murmurs and decrease in the size of the spleen.

On August 14, 1956, the patient was admitted for the second and last time with a thrombophlebitis in the right calf. Laboratory studies revealed leukocytes of 1,800/mm.^{3}, with 38% neutrophils, 61% lymphocytes and 1% eosinophils. The hemoglobin was 8.0 gm. per 100 ml.; platelet count, 105,000/mm.^{3}

The peripheral blood on October 1, 1956, revealed extensive rouleau formation. The leukocyte count was 2,100/mm.^{3}, with 24.5% neutrophils, 75% lymphocytes and 0.5% basophils. The great majority of the lymphocytes were normal and mature, but occasional cells showed transition toward the morphology of plasma cells, with grayish blue cytoplasm containing vacuoles, eccentric nuclei and more solidly clumped chromatin. Some of these cells had a finer chromatin pattern than do the usual lymphocytes, suggesting immaturity. No lymphoblast forms were seen. A bone

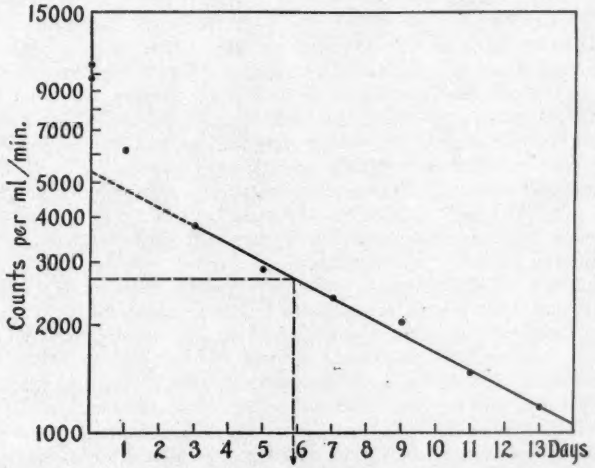

FIG. 4. The disappearance of intravenously injected I^{131}-labeled gamma globulin in case 1. The counts per minute are plotted on a semilogarithmic scale against time. One-half of the intravenously injected I^{131}-labeled gamma globulin has disappeared from the circulation in 5.9 days.

marrow specimen diluted with sinusoidal blood revealed large numbers of the same lymphocytes and transitional forms. In addition, there was some increase in the number of plasma cells, which also showed some evidence of immaturity, but definite myeloma cells could not be found. The bone marrow sections were markedly hypercellular, and it was surprising to note that the sections appeared to contain a much higher proportion of plasma cells than the marrow smears had revealed. Most of these were in a perivascular distribution, and no solid masses of plasma cells were present. It was concluded that the total picture was consistent with the diagnosis of chronic lymphatic leukemia.

Anticoagulant therapy was started August 14, 1956, and discontinued on September 25, 1956. The patient appeared to do well until October 12, 1956, when he developed low grade fever and vesicles of the lips; these, however, were amenable to topical antibiotic therapy. In November, 1956, multiple pustules appeared in the submental area, from which a nonhemolytic, coagulase-negative micrococcus was

cultured. Again, these responded to antibiotic therapy. Epistaxis was noticed at this time.

On December 2, 1956, the patient suddenly developed a fever of 104° F., with a cough productive of purulent, bloody sputum. Sticky râles were heard in the right upper chest. The leukocytes were 950/mm.^{3}, with 22% neutrophils and 78% lymphocytes. Culture of the blood and sputum yielded *Escherichia coli.* In spite of antibiotics, cortisone and metaraminol (Aramine), the patient rapidly became apathetic, tachypneic and hypotensive. On the following day the leukocytes were 2,200/mm.^{3}, with 87% neutrophils and 13% lymphocytes; the platelet count was 12,000/mm.^{3} The bleeding time was 6′ 00″, the clotting time 21′ 30″. A portable chest x-ray revealed mottled densities throughout the right lower lung field and a fan-shaped area of patchy and mottled densities about the left hilum.

Five minutes before death a profuse outpouring of blood occurred from the mouth and nose.

The pertinent autopsy findings were as follows: The heart weighed 425 gm.; the coronary arteries were patent. There were moderate thickening and scarring of the mitral valve leaflets. The left lung weighed 1,150 gm.; the right, 1,000 gm. There were three areas of infarction in the upper lobe of each lung. Nonadherent emboli were present in the branches of the pulmonary arteries supplying these areas. The liver weighed 2,425 gm. and appeared pale. The gall-bladder contained two faceted, dark brown calculi. The spleen weighed 775 gm. and was soft. The cut surface was dark red and the normal markings were obscured. There were several small, soft mucosal nodules in the stomach, measuring up to 3 mm. in diameter. No remarkably enlarged lymph nodes were observed.

Microscopic examination showed a hyperplastic bone marrow inundated by small lymphocytes of relatively uniform size. Plasma cells were only slightly increased in number. No abnormal crystals were noted. Sections of the liver, spleen, lymph nodes and other organs revealed no further evidence of leukemia or malignancy. The splenic enlargement was explained by the heavy congestion with blood. The lymphoid tissue of the spleen was relatively decreased in amount. The nodules in the gastric mucosa were benign adenomatous polypi. There was no evidence of inflammatory activity in the scarred mitral valve. The pulmonary infarcts appeared to be quite recent in origin. Section of one small bronchial lymph node revealed accumulation of budding, periodic acid Schiff-positive, yeast-phase fungi with large, empty capsular spaces, indistinguishable from *Cryptococcus neoformans.* These organisms were not found in any other tissue.

Case 2. A 65 year old white male feed salesman, admitted on August 28, 1956, had been in good health until six months prior to admission, when he had noted fatigue. For approximately two months an increase in the size of his neck had been noted, and his spleen had become palpable. A biopsy of a left supraclavicular node was interpreted as lymphosarcoma (figure 5). He was treated with "spray" x-rays for three consecutive days, resulting in a decrease in the size of his neck and spleen. Since this therapy the patient had noted pain in the upper abdomen radiating to the back and left scapular region and requiring codeine and Demerol for relief. Nine days prior to admission he had become mentally confused, with complaints of retro-orbital headaches radiating to the occiput. He then developed weakness of the left arm and leg, distortion of the left side of the face, and aggregation of food in the left buccal cavity. A "blind spot" in the left visual field also was noted. He had had poor appetite and had lost 45 pounds.

Past medical history disclosed that the patient had suffered a skull fracture in 1934 and had been semistuporous for two months. He had had several operative procedures for chronic sinusitis. For approximately nine months he had noted nocturia, hesitancy, urgency, frequency and narrowing of the urinary stream.

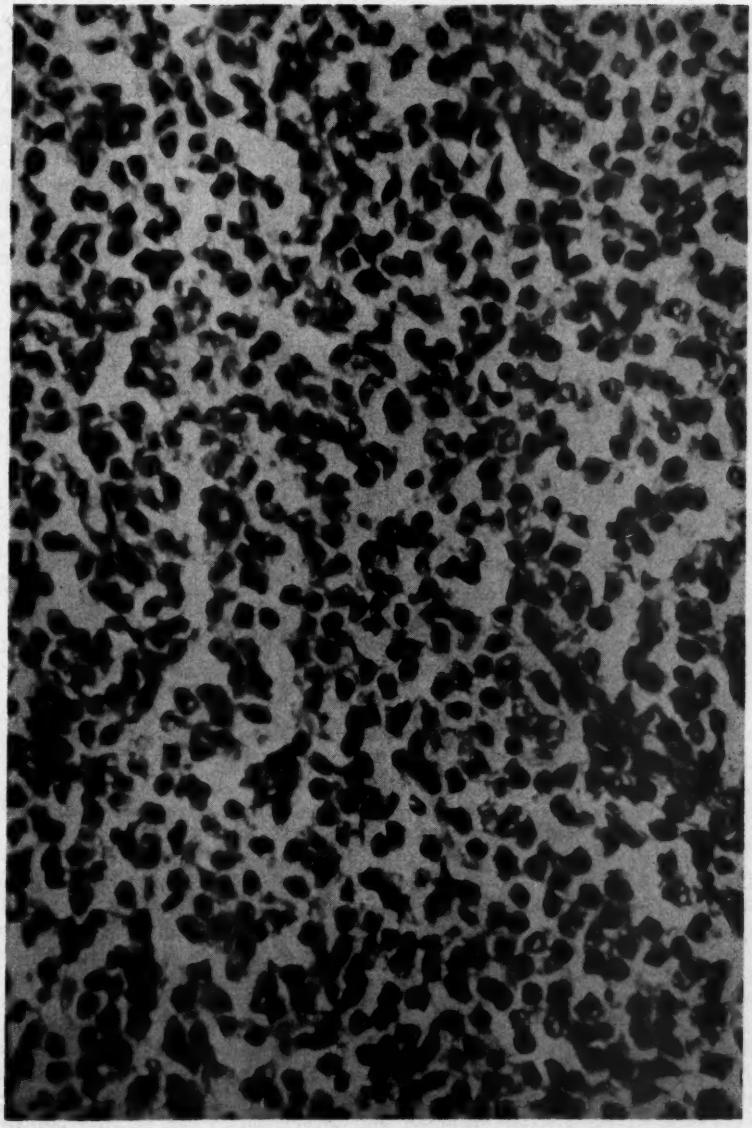

FIG. 5. Photomicrograph, magnification × 375, showing uniform infiltration of a cervical lymph node of case 2 with mononuclear cells, giving the appearance of a lymphosarcoma.

Physical examination revealed a well developed, chronically ill-appearing white male with obvious paresis of the left extremities and the left facial muscles. He was fairly alert and coöperative but demonstrated poor recent memory. On occasions he became belligerent and verbose. The temperature was 100.2° F. rectally, the pulse rate 82 per minute, and the blood pressure 130/98 mm. Hg. Punctate hemorrhages and mild early papilledema were noted in the left fundus. Small hard, firm anterior cervical lymph nodes were palpable. Fine crepitant râles were heard at the lung bases. The heart was normal. The liver extended 5 cm. below the right costal margin; the spleen was not palpable. The prostate was enlarged. Neurologic examination revealed a left temporal homonymous hemianopsia, anisocoria with the left pupil larger than the right, and paresis of the left fifth, tenth, eleventh and twelfth cranial nerves. There was a left hemiparesis with slightly hyperactive deep tendon reflexes. The Hoffman sign was positive bilaterally, and the Babinski sign was positive on the left. The left arm and face demonstrated impaired sensation to light touch and pinprick.

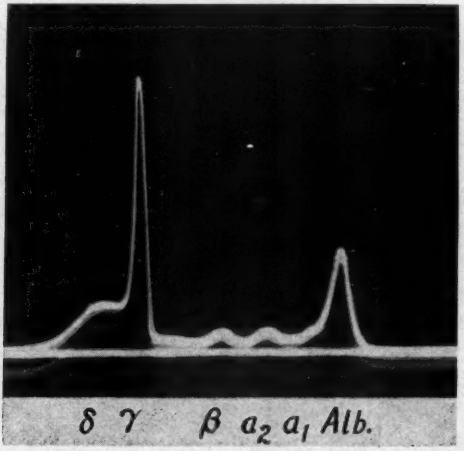

FIG. 6. Electrophoretic pattern (Tiselius) of the serum of case 2, showing an abnormal peak at the mobility of gamma globulin, similar to that in case 1.

The urine was grossly bloody and showed proteinuria. The leukocytes were 9150/mm.^{3}, with 80% neutrophils, 15% lymphocytes, 3% monocytes, 1% eosinophils and 1% basophils. The hemoglobin was 12.0 gm. per 100 ml., and the sedimentation rate was 2 mm./hour (Westergren). The red blood cell indices were: MCD, 7.4 micra; MCC, 35%; MCH, 37 micromicrograms; MCV, 108 cu. micra. A smear of the peripheral blood revealed a shift to the left of the neutrophils and rouleaux formation. The reticulocyte count was 1.1%; platelet count, 48,000/mm.^{3} The clot retraction was normal; bleeding time, 4′ 30″; clotting time, 21′. The prothrombin time was 14.9 seconds, with a control of 12.5. The prothrombin consumption was normal. Cold agglutinins were absent; however, cold red blood cell macroagglutinins were present, and the Sia water test for euglobulins was strongly positive.

The blood urea nitrogen was 18 mg. per 100 ml.; total serum protein, 14.4 gm. per 100 ml., with 2.7 gm. albumin and 11.7 gm. globulin. Serum electrophoresis revealed an albumin fraction of 3.0 gm.; alpha-1-globulin, 0.5 gm.; alpha-2-globulin, 1.1 gm.; beta globulin, 0.8; gamma globulin, 5.9 gm. per 100 ml. The gamma

peak was high and narrow and resembled that of the first case (figure 6). Ultracentrifugation of the serum at 21.7° C. in a dilution of 1:4 with 0.5 M. sodium chloride solution showed the presence of macroglobulins at three peaks, with sedimentation constants of 13.1, 17.6 and 21.0 Svedberg units, respectively. Sedimentation constants for the albumin and gamma globulin fractions in the same experiment were 3.47 and 5.2 Svedberg units, respectively (figure 7).

Five stool specimens were negative for occult blood. The urobilinogen content of a four-day stool specimen was 234 mg./24 hours. Liver function studies revealed a direct, prompt serum bilirubin of 0.1 and a total of 0.3 mg. per 100 ml.; 3% bromsulfalein retention in 45 minutes; cephalin flocculation, 4 plus in 48 hours; thymol turbidity, 7.2 units; zinc turbidity, 42 units; alkaline phosphatase, 5 K.A. units.

An electrocardiogram revealed low voltage and changes suggestive of an acute anterior myocardial infarction. Serum transaminase determinations for the first three hospital days were 12, 11.5 and 11.5 units, respectively. X-ray films of the chest revealed a slight left ventricular prominence and normal hilar shadows. A flat film of the abdomen revealed massive hepatic enlargement and equivocal splenomegaly. A flat film of the upper abdomen revealed several gall-stones. An x-ray survey of the bones and skull was negative. An intravenous pyelogram revealed no dye in the right ureter and minimal distention of the right calyces and pelvis.

A lumbar puncture revealed an opening recumbent pressure of 170 mm. water with normal manometrics. The fluid was clear and contained 5 red blood cells per

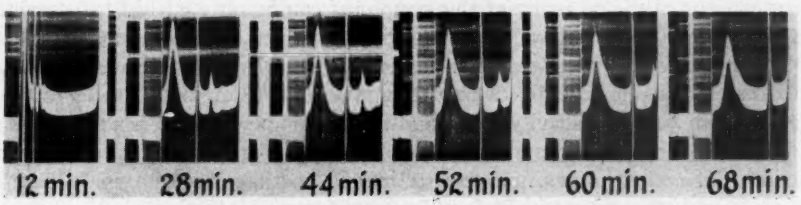

FIG. 7. Ultracentrifugation of the serum of case 2, showing separation of the macroglobulins, progressing at the indicated intervals.

milliliter. The total protein was 94.5 mg. per 100 ml.; chlorides, 122 mEq./L.; colloidal gold curve, 5554321000. Cultures for bacteria and fungi and examination for tumor cells were negative.

A sternal marrow puncture was performed with some difficulty on the seventeenth hospital day. The specimen was greatly diluted with sinusoidal blood. The distribution of the cells was normal save for a slight increase in the number of plasma cells, none of which resembled myeloma cells. No obvious lymphocytoid cells were present.

On the fourth hospital day the patient was given 28 mg. of nitrogen mustard intravenously in one dose (0.4 mg./kg.), and was started on 50 mg. of prednisone daily in divided doses. His status remained fairly stationary until the eleventh hospital day, when improvement in alertness and neurologic symptoms was first noted. The visual field defect could no longer be elicited. The total serum protein was now 10.3 gm. per 100 ml. with 1.9 gm. albumin and 8.4 gm. globulin. The leukocytes were 4,000/mm.^{3}, with 62% neutrophils, 26% lymphocytes, 11% monocytes and 1% basophils. The sedimentation rate rose to 42 mm./hour (Westergren), and the platelet count to 200,000/mm.^{3} Urinalysis revealed 1 plus proteinuria, 2 to 3 white blood cells and 15 to 20 red blood cells per high power field.

The patient continued his rather remarkable recovery. The course was complicated only by a urinary tract infection with *Aerobacter aerogenes*. Meanwhile, the

dose of prednisone had been gradually decreased and the patient began physiotherapy. On the thirty-second hospital day he was sent home for one week, walking and cheerful. On returning, he reported that he no longer required a cane for walking. He demonstrated good strength in his left extremities. On his forty-fifth hospital day the total serum protein was 9.6 gm. per 100 ml., with 2.0 gm. albumin and 7.6 gm. globulin. The deep tendon reflexes were now equal and active, and the Babinski signs were absent bilaterally. Slight left lower facial paresis and left hemiparesis were still present. At the time of discharge the patient was instructed to take 15 mg. prednisone every day.

The patient was re-admitted six weeks later, feeling well except for recent mild epigastric distress and dark stools. He had gained 15 pounds in weight. Laboratory work revealed a hemoglobin of 15.1 gm. per 100 ml.; leukocytes, 7,900/mm.^{3}, with a normal differential; sedimentation rate, 28 mm./hour (Westergren). The total serum proteins were 10.2 gm. per 100 ml., with 2.6 gm. albumin and 7.6 gm. globulin. Several stools were negative for occult blood. The patient was discharged three days later and instructed to take 12.5 mg. of prednisone daily.

Discussion

Two patients whose sera contained macroglobulins have been presented. The exact diagnosis even after autopsy of one case is still not clearcut. The first patient exhibited many of the symptoms commonly ascribed to patients with macroglobulinemia of unknown etiology. The manifestations of macroglobulinemia include weakness, asthenia, lassitude, dyspnea, weight loss, painless lymphadenopathy, edema urticaria and vascular disturbances of the extremities (cold-sensitivity, Raynaud-like phenomena, poor healing of leg ulcers).[1-12] Bone pain is absent. A bleeding tendency may manifest itself in petechiae, ecchymoses, purpura, retinal hemorrhages, epistaxis, bleeding gums, and hemorrhages involving the central nervous system or the gastrointestinal tract. Some patients have been reported to be subject to repeated infections,[5-9] as was our first case terminally. One wonders whether the large amount of abnormal gamma globulin may have been associated with a diminution of normal gamma globulins and decreased synthesis of antibodies. This would be similar to the situation found in multiple myeloma, where a relative hypogammaglobulinemia may be encountered in spite of the presence of large amounts of abnormal globulins with the motility of gamma globulin.[13]

Macroglobulinemia has been found alone or in association with hepatic cirrhosis,[11] nephrosis, disseminated lupus erythematosus, congenital lues, Sjögren's syndrome, extramedullary plasmacytoma,[3, 7, 9] multiple myeloma,[3, 14] carcinoma of the uterus,[3, 8] skin cancer, bronchogenic carcinoma[8] and sarcoma.[14] Our second case may represent one of lymphosarcoma associated with macroglobulinemia. The frequent association of macroglobulinemia with neoplastic processes has been emphasized previously.[3, 8, 15]

Characteristic laboratory findings in macroglobulinemia are an excessively elevated erythrocyte sedimentation rate,[1, 3-5, 7, 12, 15] rouleaux formation[1, 3, 10] and a normochromic, normocytic anemia which is refractory to treatment with vitamin B_{12} or iron. The sedimentation rate of our second

case may have been slowed by the exceptionally high viscosity and specific gravity; as this was reduced, the sedimentation rate rose. Electrophoresis of the serum demonstrates a high narrow peak with the mobility of gamma or beta globulin, identical in appearance with the peak encountered in multiple myeloma.

Intravascular hemolysis has been reported in two instances.[3, 9] Our first patient also had an anemia with a hemolytic component.

Although a hemorrhagic tendency has been noted in most cases of macroglobulinemia, it has not been related to a common denominator. The blood platelets, bleeding time, clotting time and prothrombin levels have been found normal [2, 5, 11] or abnormal.[3, 1, 6] Fibrinogenopenia,[1] a positive capillary fragility test [6, 15] and diminished AC-globulin with delayed clot retraction [6] have been reported.

The suspected coagulation defect has been attributed to an interference of the paraproteins with the conversion of fibrinogen to fibrin,[6] lack of prothrombin and factor VII,[10] and endotoxic or hyperergic damage to capillary endothelium.[2] Long and his associates [10] found that the addition of macroglobulin to normal sera resulted in an increased prothrombin time; the addition of distilled water to a macroglobulinemic serum resulted in precipitation of macroglobulins, a normal concentration of prothrombin, proaccelerin and proconvertin. Jim and Steinkamp, however, encountered no antagonistic effect of macroglobulin upon the clotting mechanism.[3]

The serum of both patients described here contained a small amount of macroglobulin, with a higher sedimentation constant than that of the abnormal peak. This has been described previously as a normal finding,[4] and we have encountered it in random specimens of sera without macroglobulinemia.

The ultracentrifuge experiments were single runs in each case, and are insufficient as a basis from which to calculate values of sedimentation constants under the standard conditions commonly reported, i.e., at infinite dilution of the protein at 20° C. and in water alone as the solvent. However, if the S_{20w} value for the albumin fraction is taken as that reported by Oncley, Scatchard and Brown,[17] namely, 4.6 Svedberg units, and if it is assumed (1) that the observed values of S for the albumin component in the present experiments correspond to this S_{20w} value, and (2) that the S to S_{20w} values of the other components are in the same ratios as are observed for the albumin component, then the S_{20w} values for each of the other component proteins in each case can be estimated. The observed value of S for the albumin component in cases 1 and 2, respectively, was 3.71 and 3.47 Svedberg units. Multiplying the observed S values of the other component by the ratios 4.6/3.71 and 4.6/3.47, respectively, yields the following S_{20w} values: In case 1, the gamma globulin, Waldenström macroglobulin and (normal) macroglobulin components have S_{20w} values of 6.95, 17.1 and 25.2 Svedberg units, respectively. In case 2, the gamma globulin, Waldenström macroglobulin, and the two other macroglobulins show S_{20w} values of 6.9, 17.4,

23.3 and 27.8 Svedberg units, respectively. Thus the S_{20w} values of the Waldenström macroglobulin are in good agreement in the two cases. The molecular weight of a protein possessing a sedimentation constant of 17 Svedberg units falls between 5×10^5 and 1×10^6, depending upon its molecular shape and degree of hydration.[18]

Coexistence of macroglobulins with cryoglobulins and the existence of macroglobulins alone have been described repeatedly.[5, 9, 20, 21]

In the course of the ultracentrifuge studies an observation was made which may prove to be of considerable significance regarding the nature and source of the macroglobulin component of these abnormal sera. Addition of a sulfhydryl compound, such as mercaptoethanol (0.3 ml. of 1.0 M mercaptoethanol to 10 ml. of serum), caused a noticeable decrease in the turbidity of the serum. When this serum was examined in the ultracentri-

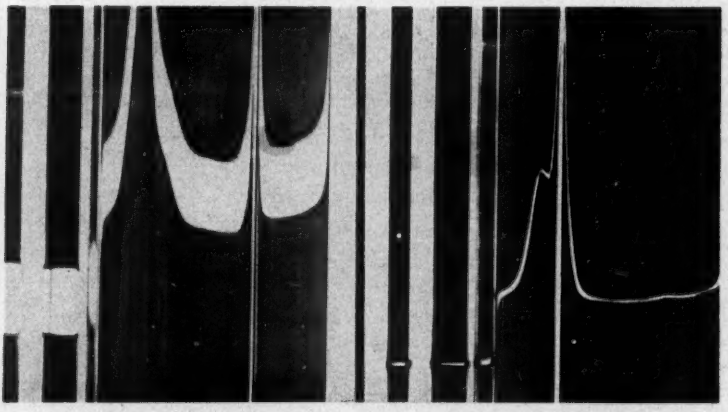

FIG. 8. Ultracentrifugal pattern of the serum, case. 1. The figure at the left shows the macroglobulin peak to the right of the normal serum proteins. The figure at the right shows the pattern of the same serum after addition of mercaptoethanol. The macroglobulin peak has disappeared and its disaggregation products now have sedimented with the constant of gamma globulin.

fuge after standing at room temperature for about an hour, it was found that the macroglobulin component(s) were no longer present and that all of the disaggregation products of the macroglobulins sedimented with a constant equal to that of normal gamma globulin (figure 8). From this it is apparent that the macroglobulins are polymers of a protein unit of the same molecular dimensions as those of the normal gamma globulins, and that the polymer cross linkage involved in their formation is of the nature of a sulfur-sulfur (cystine) bond. The main or characteristic macroglobulin component contains about six of the monomers of the size of the gamma globulin molecules.*

* After submission of this manuscript a similar observation was reported by Deutsch, H. F., and Morton, J. I., in Science 125: 600, 1957.

Splenomegaly was found in case 1, a finding similar to that of most observers. Available pathologic specimens in other cases showed an increase in size and number of malpighian corpuscles.[3, 8, 10] Such was not the finding in our one autopsied case.

Waldenström believes that the diagnosis of macroglobulinemia can be made from the characteristic bone marrow alone.[1, 14] It is typically hypocellular. Indeed, authors of previous papers have remarked on the number of unsuccessful attempts at marrow biopsy;[1, 2, 8, 12] our experience was similar in both patients.

A bone marrow specimen obtained by means of biopsy may be normal,[4, 5, 7] but most specimens are abnormal, typically showing an invasion of small, noncharacteristic lymphocytoid cells.[1, 3–6, 10–12, 15, 19] These cells may be described as resembling both lymphocytes and plasma cells. Typical mature plasma cells may be present[4, 5] or even increased,[8] as was the case in our first patient.

Numerous lymphocytoid cells have been found in the peritoneum, pancreas, urinary bladder, subcutaneous tissue, liver and kidney of patients with macroglobulinemia.[5, 8, 10, 11] Our one autopsied case showed this finding in the bone marrow only.

Retinal hemorrhages such as were seen in our patients are not necessarily an expression of a generalized hemorrhagic tendency, but may be found in any patient with a profound anemia. The neurologic disturbances in our second patient, in addition, were very likely an effect of intracranial thrombosis. We are impressed with the hemolytic character of the anemia in case 1, evidenced by the increased fecal urobilinogen and the presence of cold macroagglutinins.

It should be emphasized that macroglobulinemia is probably the result of some diffuse injury to the reticulum and should not necessarily be considered a disease per se. We are uncertain, even after necropsy, whether case 1 is that of a "primary" or idiopathic macroglobulinemia or a leukemic process. Most certainly the course revealed it to be a malignant disease. The second case provided us with a lymph node biopsy which was indistinguishable from lymphosarcoma. Since the lymphocytoid infiltration of a lymph node in a patient with "primary" macroglobulinemia may present the same picture, the diagnosis of the underlying pathology in the second case remains a matter of conjecture. It would seem that macroglobulins are the result of an abnormality of protein production wrought by an underlying primary disease.

Addendum

The second patient has been followed for 21 months now. Under a daily maintenance dose of 12.5 mg. of predisone he has remained asymptomatic. The total serum proteins have decreased to 9.0 gm./100 ml., with an albumin increase to 3.1 gm./100 ml. and a decrease of macroglobulin to 3.7 gm./100 ml.

Summary

Two cases have been presented exhibiting macroglobulinemia. In the first patient the underlying fatal disease may have been a chronic lymphatic leukemia, although this point could not be proved satisfactorily. This patient's ability to form antibodies against bacteria seemed impaired. The final chapter of his illness was characterized by bacterial infections and bacteremia. The presence of *Cryptococcus neoformans* in a lymph node reminds us of the relatively frequent association of this yeast with lymphoblastomas. The first patient had an anemia which was hemolytic in character and did not respond to therapy with iron, liver extract or vitamin B_{12}. The intestinal absorption of radioactive cobalt-labeled vitamin B_{12} was normal. The second patient is surviving. At one time he showed signs of probable intracranial thrombosis. His subsequent clinical course might clarify the etiologic aspect of his macroglobulinemia. The finding of macroglobulinemia does not necessarily constitute a definitive diagnosis. Frequently it reveals itself as a secondary phenomenon, related to an underlying disease, which causes diffuse injury to the reticuloendothelial system. One of our laboratory observations may shed light on the nature of the macroglobulin molecule.

Acknowledgment

The writers are indebted to Miss Janet Johnson for her technical assistance.

Summario in Interlingua

Es presentate le casos de duo patientes con macroglobulinemia. In ambes le macroglobulinas ha le mobilitate electrophoretic de globulina gamma. Globulina gamma marcate con I^{131} e injicite intravenosemente in le prime del patientes revelava un accelerate disparition de globulina gamma normal. Le prime del duo patientes habeva un anemia hemolytic e un reducite capacitate a formar anticorpore, e le capitulo final de su morbo esseva characterisate per infectiones bacterial e bacteremia. Le constatationes al necropsia esseva constatationes de un chronic leucemia lymphatic. *Cryptococcus neoformans* habeva invadite un del nodos lymphatic que esseva examinate histologicamente.

Le secunde patiente con macroglobulinemia supervive post un episodio de thrombose intracranial. Ille habeva un lymphadenopathia, le qual—insimul con le defectos neurologic—respondeva dramaticamente al tractamento con mustarda a nitrogeno. Le biopsia de un nodo lymphatic revelava un aspecto compatibile tanto con lymphosarcoma como etiam con macroglobulinemia primari.

In le curso de studios a ultracentrifugation, il esseva notate que le addition de mercaptoethanol (0,3 ml de un solution de 1,0 M a 10 ml del sero) resultava in le dispolymerisation del macroglobulina. Le productos de disaggregation del macroglobulinas se sedimentava con un constante que esseva equal al constante de globulina gamma normal. Iste constatation rende apparente que le macroglobulinas es polymeros de un unitate proteinic del mesme dimensiones molecular como globulinas gamma normal e que le connexiones transversal del polymero in question es del natura de un ligamine de sulfure a sulfure (cystina). Le componente principal o characteristic de macroglobulina contine circa sex monomeros del dimension de moleculas de globulina gamma.

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SCREENING FOR CARDIOVASCULAR DISEASE IN BALTIMORE*

By Charles M. Wylie, M.D., Dr.P.H., *Baltimore, Maryland*

In the last 20 years medical and public health authorities have recognized cardiovascular disease as an increasing problem, the control of which requires both organized community and individual action.

Ten million persons in the United States are estimated to have cardiovascular disease, which causes one out of every two deaths.[1] Patients with these long-term diseases lose many workdays and have much permanent disability. These facts increase the importance of cardiovascular disease as a community problem.

Statistics for this group of diseases are based on the incidence and prevalence of diagnosed cases. However, some apparently well persons can have early cardiovascular disease, just as they have diabetes and pulmonary tuberculosis. Only small numbers of them visit their physicians for routine examinations. Some cardiovascular disease will therefore progress undetected to a later stage at which medical care is less effective.

Multiple screening may help in early detection. Screening tests are procedures that sort out persons who probably have abnormalities from those who probably do not.[2] Multiple screening is the simultaneous use of two or more screening tests. Persons with positive tests are referred to their physicians for diagnosis and treatment if necessary. Effective multiple screening allows physicians to concentrate their "routine" physical examinations on persons (with abnormal screening tests) who are more likely to have cardiovascular disease than do other asymptomatic persons.

This paper will discuss some problems in screening for cardiovascular disease, and will briefly present the results of four screening tests used in Baltimore, Maryland.

The Questionnaire

In theory, screening tests should screen persons who are symptom-free. In practice, however, screenees may have symptoms which they believe do not justify a visit to their physicians. A questionnaire can therefore have a place in screening. Its several questions on symptoms would have to be positive for most persons with cardiovascular disease, and negative for most of those without disease.

The Cornell Medical Index is the best known questionnaire in current use. However, when used on clinic outpatients and when interpreted

* Received for publication March 8, 1957.

Requests for reprints should be addressed to Charles M. Wylie, M.D., The Johns Hopkins University School of Hygiene and Public Health, 615 North Wolfe Street, Baltimore 5, Maryland.

by physicians, the index was found to identify wrongly 30 diagnostic areas in each 100 patients.[3] The false-positive results prevent its effective use in screening "healthy" persons.

Phillips and associates [4, 5] have produced a helpful study of questionnaires for detecting heart disease. Several of their questions caused large numbers of false-positive results. Two questions were more effective than the others, however:

1. Do you ever have distress, pain or an uncomfortable feeling in the chest while walking on the street or up inclines or steps?
2. While walking are you forced to stop in order to rest?

The screening clinic in Baltimore used only these two questions. To keep the number of wrong referrals to a minimum, screenees were sent to their physicians only when both answers were affirmative. This report will later present the results of this plan.

The 70 mm. Chest Roentgenogram

The posteroanterior chest roentgenogram has been widely used to screen for cardiac conditions. Miniature chest films, taken primarily to detect early pulmonary tuberculosis, have been read for cardiovascular conditions at little extra expense.

The chest roentgenogram will often provide only suggestive evidence of a heart abnormality. No specific shape of the heart is pathognomonic of a particular kind of heart disease. However, the chest x-ray can show the size of the heart better than any other method.

The posteroanterior chest film can seem normal even when the heart is enlarged. Slight scoliosis or slight rotation of the patient may cause a falsely positive reading of heart enlargement. Moreover, heart disease may not cause enlargement. It is to be expected, therefore, that the chest roentgenogram will be a screening method with low sensitivity (missing many cases of disease), and low specificity (producing many false-positive results).

Anderson has suggested that film readers who pay particular attention to cardiovascular shadows will greatly increase the yield of heart cases. However, a joint committee of the American Public Health Association, National Tuberculosis Association and the U. S. Public Health Service has recommended against using special readers for heart disease.[6] The screening clinic in Baltimore followed this recommendation. One chest physician read films for abnormalities of both lungs and heart.

The Electrocardiogram

Patients with heart disease often have normal electrocardiograms. Furthermore, some persons without other evidence of heart disease have

abnormal tracings. Some physicians [7, 8] question whether electrocardiographic abnormalities found on routine examination of apparently well subjects have the same significance as abnormalities in patients with clinical findings of heart disease. For instance, Wilson and associates [8] stress that electrocardiographic abnormalities are not diseases.

Two recent studies [4, 9] show that the 12-lead electrocardiogram has many false-positive results. The Lead I tracing used alone causes even more false-positives.[9, 10] However, Witham and Jones [11] have reported more favorably on the value of the electrocardiogram in screening.

The screening clinic in Baltimore used the electrocardiogram, since the test was apt to detect some patients with heart disease who would otherwise remain undiscovered. Technicians took the three bipolar and three augmented unipolar limb leads while the screenees were lying down. Thus the screenees did not have to undress at all.

A cardiologist classified each tracing (which bore the subject's age and blood pressure) as normal, doubtful or abnormal. The revised recommendations [10] of the Framingham Epidemiology Study guided the cardiologist in classifying the tracings. Screenees with doubtful readings were invited to return for 12-lead electrocardiograms, which were used to classify the results finally as normal or abnormal. The screenee was referred to his physician when the 12- or six-lead tracing was abnormal, or when the six-lead tracing was doubtful and the screenee failed to return for the rescreening test. The results are given later in this report.

The Blood Pressure Reading

Of the estimated 10 million persons with cardiovascular disease, about 4.6 million have high blood pressure.[1] Pickering has recently stressed that a high blood pressure does not always indicate a pathologic process.[12] Whether or not hypertension is a "disease," it is certainly accompanied by a rise in mortality. The value of screening for hypertension will therefore depend on whether early medical supervision will delay the changes that lead to the hypertensive patient's final disability and death. The benefits of discovering hypertension early have been neither proved nor disproved as yet.

The test best suited to screen for hypertension is the indirect measurement of blood pressure. Since individual sphygmomanometric readings have a mean error of $\pm$ 8 mm. Hg,[13] the screening levels in Baltimore were set high to prevent too many false-positive results. Master, Garfield and Walters [14] suggest that the upper limits of "normal" pressure increase with age. Based on their figures, the Baltimore screening levels were:

150/90 for persons under 35 years.
160/96 for those 35 through 49 years.
170/100 for those 50 years or older.

TABLE 1

Results of Screening for Cardiovascular Disease and of Follow-up with the Physician by Sex of Persons Screened. (Results expressed in rates for each 1,000 screened)

Screening and Follow-up Results	Questionnaire		Chest X-ray		Electrocardiogram		Blood Pressure	
	Men	Women	Men	Women	Men	Women	Men	Women
Number screened	1000	1000	1000	1000	1000	1000	1000	1000
Positive	41	76	109	98	123	121	71	77
Disease unknown to screenee	19	60	93	83	95	97	35	32
Follow-up with MD completed	10	32	39	37	59	68	22	19
Disease confirmed	7	11	16	17	23	20	14	16
Previously unknown to MD	0	5	5	4	10	6	5	6

The individual was referred to his physician if both systolic and diastolic pressures were above those levels. The screenee was also referred if the systolic pressure alone was 20 mm. Hg or more above the screening level, or if the diastolic pressure alone was 10 mm. Hg or more above the screening level.

SCREENING RESULTS

The screening program in Baltimore tested more than 2,000 persons for cardiovascular disease and for a number of other conditions. Another report [2] has described this program more fully. When previously interviewed at home, most persons reported that they were healthy or that they had only minor ailments. A small number reported more serious conditions.

The clinic staff asked each person if he had heart disease or high blood pressure. Screenees replying "yes" were not referred if the corresponding test was positive. This procedure reduced as much as possible the referral

TABLE 2

Results of Screening for Cardiovascular Disease and of Follow-up with the Physician by Age in Years of Persons Screened. (Results expressed in rates for each 1,000 screened)

Screening and Follow-up Results	Questionnaire		Chest X-ray		Electrocardiogram		Blood Pressure	
	44 or under	45 or older	44 or under	45 or older	44 or under	45 or older	44 or under	45 or older
Number screened	1000	1000	1000	1000	1000	1000	1000	1000
Positive	28	119	38	223	59	230	32	160
Disease unknown to screenee	23	79	35	184	53	168	19	59
Follow-up with MD completed	8	47	11	86	26	126	12	36
Disease confirmed	2	22	2	45	2	57	8	29
Previously unknown to MD	1	6	1	12	1	19	4	8

of patients whose heart disease or hypertension was already known to their physicians.

To obtain the follow-up results, the staff got in touch with each referral. When he reported that he had sought medical advice, the clinic staff obtained the diagnostic result from the physician. Table 1 presents these results in rates for each 1,000 persons screened.

TABLE 3

Positive Results of Each Test, by Race and Sex of Persons Screened.
(Results expressed in rates for each 1,000 screened)

Screening Test	Total Persons Screened	White		Non-White	
		Men	Women	Men	Women
Questionnaire	1000	41	68	37	98
Chest X-ray	1000	94	70	178	186
Electrocardiogram	1000	118	109	152	153
Blood Pressure	1000	58	60	124	129

The electrocardiogram produced the greatest yield of previously unknown cases, while the questionnaire had the smallest. The chest roentgenogram and blood pressure tests had intermediate yields. The specificities of the tests were satisfactory; none had more than two false-positives for each true-positive result among screenees who completed follow-up.

TABLE 4

Comparison of Obesity, and Electrocardiographic and Blood Pressure Test Results, by Sex of Persons Screened

Degree of Obesity, by Test Result	Electrocardiogram		Blood Pressure	
	Men	Women	Men	Women
Total screened	921	1095	921	1095
Per cent abnormal	11.0	10.3	7.1	7.7
Non obese	667	831	667	831
Per cent abnormal	8.2	9.1	5.1	5.5
Moderately obese	133	97	132	94
Per cent abnormal	11.3	16.5	9.1	8.5
Severely obese	121	167	122	170
Per cent abnormal	25.6	12.6	15.6	17.6

The questionnaire was much less sensitive than were the other tests, since it missed many cases which were picked up by the other tests.

Sex: The questionnaire found more previously unknown cases in women than in men. The sex of the screenees did not significantly change the results of the other tests.

Age: Table 2 shows that positive results and confirmed cases rose greatly with increasing age. Indeed, the confirmed cases detected by the questionnaire, chest roentgenogram and electrocardiogram were confined mainly to those over 44 years, and by the blood pressure test to those 30 years and older.

Race: Table 3 compares the results in white and Negro screenees. Negroes gave about one and one third times as many positive results with the chest roentgenogram and blood pressure test as did white screenees. The increased yield in Negroes occurred in both sexes.

Obesity: Technicians measured the height and weight of each screenee. When the weight was 30% or more above the central figure of the Metropolitan Life Insurance Tables,[15] the screenee was classified as "severely obese"; those between 20 and 29% were "moderately obese"; those under 20% were "nonobese."

Table 4 shows the results obtained for obese persons. The questionnaire (not shown in this table) produced more positive answers with increasing obesity, but the relationship was not close or significant. The proportion of positive electrocardiographic tracings and blood pressure readings rose significantly as obesity increased. These changes occurred in both sexes. The survey did not study the effect of obesity on the chest x-ray readings.

Discussion of Test Results

The screening levels of the tests in Baltimore were deliberately chosen to prevent large numbers of false-positive results. The tests were therefore insensitive, particularly the questionnaire, which missed many patients whom other tests detected.

Some clinicians may prefer to find large numbers of false-positives in order to miss fewer cases. However, one must consider the cost of diagnosis in evaluating the problem of false-positives. It is often costly to prove that a positive result such as that of the electrocardiogram is false. Screening programs will fall into disrepute if they cause large numbers of persons to undergo expensive diagnostic examinations unnecessarily. Furthermore, persons missed by cardiovascular tests are less likely to progress rapidly to an incurable stage than would those, for instance, with lung carcinoma.

Although the Baltimore program took precautions to prevent referral of previously known cases, the physicians were aware of two thirds of the confirmed cases. This situation reduced the "yield" of the tests, since mainly the previously unknown patients benefited by their discovery. A more effective method must be found to reduce this administrative problem.

Conclusions and Summary

The chest roentgenogram, electrocardiogram and blood pressure tests are sufficiently effective to be included in future screening programs. The

results of the questionnaire in Baltimore and in other programs have been unsatisfactory.

To reduce the cost of multiple screening, future programs may test groups in which the prevalence of disease is high. The Baltimore results show that cardiovascular tests have a higher yield when confined to persons 45 years and older, to Negroes, and to overweight persons.

The Baltimore study shows that screening apparently well persons will detect previously unknown cases of cardiovascular disease. The study does not show that newly diagnosed patients will necessarily benefit by their early discovery. This paper briefly mentions other aspects—such as the problems of setting screening levels and of referring only previously unknown cases—which need further investigation.

SUMMARIO IN INTERLINGUA

Le precoce detection de morbo cardiovascular es sin dubita de valor potential in le subjugation de iste serie problema sanitari. Pro verificar iste theoria, quatro tests de detection esseva applicate a 2.000 subjectos adulte le majoritate del quales se considerava como essentialmente san.

Le prime test consisteva de duo questiones relative a disconforto physic post effortio. Responsas affirmative a ambe iste questiones esseva classificate como anormal.

Le secunde test esseva un roentgenogramma thoracic de 70 mm, scrutate pro anormalitate de dimension o de conformation del corde.

Le tertie test consisteva de sex electrocardiogrammas, tres derivationes bipolar e tres derivationes unipolar augmentate de extremitates. Le classification del datos esseva effectuate per un cardiologo.

Le quarte test consisteva de determinationes del pression sanguinee. Istos esseva classificate como anormal quando illos amontava a plus que 150/90 mm de Hg in personas de minus que 35 annos de etate, a plus que 160/96 mm de Hg in personas de inter 35 e 49 annos de etate, e a plus que 170/100 mm de Hg in personas de plus que 50 annos de etate.

Subjectos con resultatos anormal qui non sapeva que illes habeva morbo cardiovascular esseva exhortate a consultar lor medico de familia. Subsequentemente le diagnose del medico esseva obtenite.

Le prime del tests, i.e. le questionario, non se provava efficace in le detection de morbo cardiovascular. Le tres altere tests, i.e. le roentgenogramma thoracic, le electrocardiogramma, e le determination del pression sanguinee, esseva plus satisfactori. Gruppos in que le proportion de resultatos positive esseva elevate consisteva (1) de individuos de plus que 45 annos de etate, (2) de individuos de racia negre, e (3) de individuos obese.

Tests detectori in grosso es capace a identificar previemente non recognoscite morbo cardiovascular in individuos de apparentemente normal stato de sanitate. Tamen, il remane a demonstrar que le diagnose precoce es de valor pro le patiente.

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CASE REPORTS

LSD-LIKE DELIRIUM FOLLOWING INGESTION OF A SMALL AMOUNT OF ITS BROM ANALOG (BOL-148) * †

By Nelson Richards, Loring F. Chapman, Helen Goodell, and Harold G. Wolff, F.A.C.P., *New York, N. Y.*

In 1943 Hoffmann [1] detected in himself strange mental effects from a compound that he and Stoll [2] had prepared in 1938 and reported in 1943 as an oxytocic agent similar to ergonovine. This observation of the effect of lysergic acid diethylamide (LSD) led to the investigation of other derivatives of this compound in research on experimentally induced mental disorders.[3] LSD and most of its related compounds have been found to produce an anti-5-hydroxytryptamine (serotonin) effect both peripherally and, it has been assumed, centrally by blocking the action of serotonin.[3a]

Cerletti and Rothlin [4] have reported on a compound, 2-bromo-*d*-lysergic acid diethylamide, coded BOL-148. When 0.65 mg. of this agent was given to their laboratory workers, they observed no changes in mentation similar to those produced by LSD. From this observation in 1955 they concluded that the theory of the production of mental changes being secondary to the antiserotonin action of LSD must be challenged, since BOL-148 produced no psychic symptoms.

Ginzel and Mayer-Gross [5] gave BOL-148 to volunteers for two days and observed that when LSD was given on the third day psychologic symptoms did not appear. They further observed that in three other cases, when BOL-148 was given for only one day previous to the LSD, the changes were "reduced to abortive and short lasting." When the experiment was reversed and the BOL-148 was given at the height of the LSD symptoms there were no noticeable or persistent changes in the symptoms of LSD intoxication. They concluded that BOL-148, which was closely related to LSD chemically, was effective in blocking the effects of the latter agent on mentation.

Abramson [6] has alleged that the best antidote to LSD is LSD itself. Others [7, 8] have shown that individuals given the agent on successive days developed a rapid tolerance to the compound.

Snow [9] has administered as much as 7.5 mg. of BOL to patients with metastasizing carcinoid tumors, a condition associated with the accumulation of large amounts of serotonin, without reporting mental disturbances.

The disturbances of mental function induced by LSD and some of its derivatives [3b, 10] include disturbances of affect and thought, distortions of perception

* Received for publication July 6, 1957.

From the Study Program in Human Health and the Ecology of Man and the Departments of Medicine (Neurology) and Psychiatry, The New York Hospital-Cornell Medical Center.

† Supported in part by a training grant from the National Institute of Neurological Diseases and Blindness.

Requests for reprints should be addressed to Harold G. Wolff, M.D., The New York Hospital, 525 East Sixty-eighth Street, New York 21, N. Y.

and body image, and manifestations of depersonalization. Visual illusions and hallucinations are common, though auditory hallucinations (akin to those of schizophrenic psychosis) are not. Distortions of color perception and the conversion of straight lines into undulating ones are common. When given in small amounts euphoria may occur, and in high amounts a condition resembling complete withdrawal, or "catatonia," develops.[11, 12] It is interesting to note how similar the experiences of these subjects are to those of toxic deliria from severe systemic diseases, i.e., fever, sepsis, bacteremia, uremia, hypoxia, etc. When the effects of a single administration of LSD are compared to the delirium associated with an acute systemic disease that has been given prompt etiologic treatment, the courses of the effects of the two toxins closely resemble each other, especially in their response to attempts to help the subject orient himself, to make him feel secure and to identify his surroundings.

The effects of LSD include a decrease in blood pressure and pulse rate, and an increase in body temperature, urinary output and rate, and intestinal motility.[3c] These effects may be modified if during the mental changes the individuals are very anxious.[3d] Hoch [3e] related that these symptoms occurred without the psychic manifestations, although the reverse was not observed. He suggested that this variability in response may be related to the amount of the drug given. and that the effect on the blood pressure, pulse, body temperature. etc., could "spill over into some psychic manifestations."

Since there is a variability in the production of psychic symptoms which is greater than the variability in the production of symptoms referable to blood pressure, pulse and body temperature, it is postulated that the two chemically related compounds, LSD and BOL-148, are related in pharmacologic and psychologic effects, and differ only as to the amounts necessary to produce such effects. The following is a summary of events that support this thesis.

Case Report

A moderately anxious 28 year old worker in this laboratory, who usually controlled and repressed his affective expressions, took BOL-148 during a vascular headache for the purpose of observing the effect of this agent on his headache. This man was mildly hypertensive and subject to vascular headaches. He ingested 0.5 mg. of BOL-148 approximately two hours after the onset of a moderately severe, bitemporal, "pounding" vascular headache. About 15 minutes later his mood became elevated, he sought aid for his state, and he became more and more talkative in louder and louder tones. He complained of lightheadedness and expressed the fear that he might lose consciousness. Twenty-five minutes after ingesting BOL-148 his headache was reduced in intensity. However, his head remained tender, and deep pain thresholds, which had been low at the onset of headache, were not elevated. Some 40 minutes after the agent was taken he first noted distortions of body image, i.e., he felt as though one arm were growing longer and out of proportion to the other arm, and as though his abdomen were increasing in girth. His elevated mood gave way to one of intense anxiety merging into panic, which was "controlled only by great effort of will." Tachycardia and palpitations occurred, along with nausea and finally vomiting and urgency of defecation about one hour after ingesting the agent. Most frightening for the subject, according to his utterances, was the inability to concentrate and the sensation of seeing things as smaller or out of proportion. He became clumsy, bumping into things and people in a very familiar surrounding. His speech became slurred and thick.

He reported altered color perception, in that things would change hue and thereby become very annoying. This could be abolished by closing the eyelids. The lines of bricks on the wall of the building across the court became wavy. He was restless and had a fine tremor. Tinnitus was present and persistent.

To describe the reaction more vividly, a statement of the subject's recall of the experience follows:

"Anxiety was associated principally with uncertainty about how severe the mounting reaction would become and if it might even lead to death. The impairment in mentation and possible loss of consciousness also made me fearful. The effects of stimuli in all modalities, but particularly in regard to color, were amplified. Stimuli did not necessarily seem louder or brighter than usual, but their effects were poorly modulated, they seemed to mount in intensity and threatened to block other aspects of mentation. The phenomenon was most striking in regard to visual stimuli: I would become absorbed in the color of a sign on the door or in the whiteness of the sheets on the bed. The mounting intensity of the effects of these stimuli was frightening because I had difficulty controlling it. Reactions to the sound of a refrigerator motor or of a ringing in my ears became particularly frightening, since I could not exclude them, as I could the visual stimuli, by closing my eyes. Tactile sensations also led to effects that were amplified in this way. Stroking the skin lightly at times gave rise to sensations that were hard to distinguish from those of mild burning pain. The significance of other pain, such as mild muscle cramps, became exaggerated. Affect was modulated poorly; in one instance I imagined a recurrent rhythmic musical theme which became more and more insistent, causing feelings of excitement and exaltation accompanied by weeping. Early in the reaction I believed that part of myself was intact and I could remain detached and observe the phenomenon. Later, particularly after experiencing poorly modulated affective reactions, I began to doubt that I could trust my reactions at any level. Ideas of suicide or facetious comments that might be made entered consciousness and were rejected quickly, but with a recognition that the disturbances extended through all levels of awareness."

The subject was put to bed and an examination was begun about two hours after the ingestion of the agent, BOL-148. His movements were clumsy and awkward and he had difficulty in undressing.

Examination revealed: blood pressure, 180/120 mm. of Hg; pulse, 139; respirations, 30 per minute. The patient's face and body were flushed and felt warm to the touch. His heart was not enlarged to percussion, although the beat was forceful and bounding. His mentation was "cloudy," and tests showed poor calculation of simple problems and poor "serial sevens." Orientation to time, place and person was accurate. Pupils were 3 mm. in diameter and reacted readily to light and attempts at near vision. Speech was thick and the mouth was dry, although other functions of the mouth segment were unimpaired. There was a fine tremor of the outstretched extremity but no intention tremor. Fine movements were not graceful and smooth. Deep tendon reflexes were slightly hypoactive but symmetric. There was no loss of sensory perception. The patient complained of increased intestinal motility, although no borborygmi could be heard.

During the examination, which was purposely prolonged and done in especial detail to reassure the patient, he was less anxious and had fewer visual illusions. Blood pressure and pulse rate fell to 140/90 mm. of Hg and 96 to 100 beats per minute, respectively. On being left alone even for a few moments his anxiety and visual misinterpretations increased markedly. Because of continued restlessness and anxiety he was given chlorpromazine, 10 mg. by mouth, about four hours after ingesting the BOL-148. Approximately 15 minutes later he noted return of his visual illusions, "cloudy" mentation and color misinterpretation, exactly as he had noted them at the

height of the BOL-148 effect. The increased anxiety, panic, blood pressure, pulse, rumbling in the abdomen and urgency of defecation cleared in some degree about one and a half hours later, although he still reported difficulty in concentration and recall. Headache also returned in a mild degree. This being about midnight and about seven hours after first ingesting the BOL-148, he went to sleep. No dreams were recalled.

For the next three days he observed easy fatigue, both mental and physical, and little interest in work. A given task consumed excessive energy and work efficiency was diminished.

Discussion

From these observations it is clear that BOL-148 in a relatively small amount produced a delirious reaction similar in almost all respects to that of LSD. Pupil, blood pressure and other cardiovascular changes were probably features of the subject's panic. This individual's experience calls for a reëvaluation of the statement that BOL-148 does not produce mentation changes in low dosage.

Since LSD administered for several days can block its own effects, the suggestion of Ginzel and Mayer-Gross that BOL-148 blocks the effects of LSD does not necessarily indicate a different mode of action of the two drugs, but rather the development of a tolerance interchangeably between the two agents. It is interesting that when BOL-148 was given only one day prior to LSD, minor effects of LSD were noted, i.e., tolerance had not developed.

The similarity of the effects of "psychotomimetic" drugs such as LSD, BOL-148, bufotenin, mescaline, bulbocapnine, etc., and the states produced by fever, sepsis, uremia, bromides, carcinomatosis and cerebral arteriosclerosis in some individuals, is to be emphasized. The similarity is in fact that an abnormal mental state can be produced by all, and that a chemical agent in small amounts can produce effects of short duration. All produce delirium.

In regard to the potentiation of the effect of the BOL-148 by chlorpromazine, Abramson [3f] stated in the case of LSD that the variable effect of 50 mg. of chlorpromazine by mouth on the LSD reaction was related to the time of administration of the two drugs. In at least two out of five subjects in his studies, when both agents were given at the same time there was a potentiation of the LSD reaction. Hoch,[3g] however, found that the same amount (50 mg.) of chlorpromazine intravenously abolished the effects of LSD.

Conclusions

1. BOL-148 in a relatively small amount produced LSD-like effects in a male laboratory worker.

2. The effects of both of these agents are similar to those of a toxic delirium or acute exogenous reaction.

3. The hypothesis that BOL-148 and LSD are dissimilar in regard to psychic effects but similar in regard to all other antiserotonin reactions must be revised. It is likely that they are different only in degree.

Summario in Interlingua

Le similitude inter certes del symptomas de psychose schizophrenic e le effectos de intoxication per diethylamido de acido lysergic (in le texto = LSD)—i.e. distortiones perceptual, illusiones, "hallucinationes," alterationes de imagines corporee,

alterationes de postura, e disturbationes emotional del typo de anxietate, depression, euphoria, e sensation de dispersonalisation—ha stimulate un grande numero de studios con LSD e simile agentes in le spero de obtener un plus complete comprension del natura de psychose schizophrenic.

Un varietate de iste agentes "psychotomimetic" es antimetabolitos de serotonina, un substantia que ha recentemente essite recognoscite como occurrente in le systema nervose e specialmente in le cerebro. Es suggerite que tal agentes psychotomimetic affice le systema nervose principalmente per disturbar le activitate de serotonina in le cerebro. Multes del agentes psychotomimetic es analogos structural de serotonina, e lor action antagonistic al action de serotonina pote esser demonstrate in musculo lisie in vitro.

Le rolo de serotonina in iste alterationes mental esseva questionate per le observation de Cerletti e Rothlin que diethylamido de acido 2-bromo-d-lysergic (in le texto = BOL-148) esseva un forte antagonista del effectos in vitro de serotonina sed que illo non produceva le disturbationes mental que es characteristic de LSD.

In le observationes hic reportate, un juvene adulto (un technico de laboratorio) prendeva 0,5 mg de BOL-148 per via oral. Circa un hora post le ingestion, ille experientiava un euphoria transiente, sequite per distortiones perceptual e illusiones (primarimente visual sed etiam auditori e tactile), distortiones de imagine corporee, hyper-reaction a color, sensation de dispersonalisation, sever grados de anxietate, tremor, disquietude, e defectos de mentation—i.e. concentration, memoria, calculation, subtraction serial de 7 ab 100, discrimination a duo punctos, e recognition de numeros traciate al superficie del bracio. Iste reactiones persisteva durante circa 24 horas e esseva sequite per un secunde periodo de 24 horas de leve grados de depression e de un sensation de exhaustion.

Iste disturbationes esseva identic con illos observate in casos moderatemente sever de intoxication per LSD, describite per multe altere autores e observate a iste laboratorio.

Con le exception de lor breve duration, le effectos del intoxication per BOL-148 e per LSD es typic pro le delirio classic observate in statos de febrilitate, in morbo cardiac o renal, in hypoxia o vulneration del capite, e in statos post le prolongate administration de bromuros, etc. Le mesme aspectos general del delirio es notate sin reguardo al identitate del agente causative, sed intra le limites de iste aspectos commun il occurre marcate variationes que es determinate in grande parte per le reactiones characteristic del personalitate del individuo in question, per su etate, su debilitate general, su experientias premorbide, le ambiente cultural e social, e le duration del abreaction.

Iste observationes indica que BOL-148—ben que plus grande quantitates de illo es requirite que de LSD pro producer disturbationes mental—es etiam capace, in relativemente basse quantitates, a producer disturbationes de comportamento e de mentation.

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MEDIASTINAL EMPHYSEMA: A COMPLICATION OF BRONCHOSCOPY *

By Robert N. Armen, M.D., F.A.C.P., *Brooklyn, N. Y.*, C. S. Morrow, M.B., F.A.C.P., Ch.B. (Edin.), and Stephen Sewell, M.D., *Wilkes-Barre, Pennsylvania*

Mediastinal emphysema, a clinical entity denoting the presence of air in the connective tissue of the mediastinum, was first described as long as a century ago.[1] Its significance, however, has received wide recognition only during the last 20 years or so, and a great wealth of literature has accumulated about its various aspects. Despite this fact, few articles have dealt with its occurrence as a complication of bronchoscopic procedures. The paucity of such reports might be on the basis of the rarity of this complication, or it might possibly reflect a reluctance on the part of many observers to record these unfortunate accidents. Benedict[2] cites perforation of the trachea or a main bronchus as one of the complications of bronchoscopy. Several other writers[3, 4] have described cases of mediastinal emphysema where it occurred as a result of direct injury to the main airways. A review of our records at this hospital since its opening in November, 1950, reveals a total of about 370 bronchoscopies, many

* Received for publication October 29, 1956.
From the Medical Service, Veterans Administration Hospital, Wilkes-Barre, Pennsylvania.
Requests for reprints should be addressed to Robert N. Armen, M.D., Veterans Hospital, Brooklyn 9, N. Y.

with biopsies. There is only one case on record with mediastinal emphysema as a complication. Recognizing mediastinal emphysema to be a distinct hazard to life, we are reporting this case along with a discussion of the related subjects of "pulmonary interstitial" and "subcutaneous" emphysema. It is also our purpose to suggest the possibility that a mechanism other than traumatic perforation

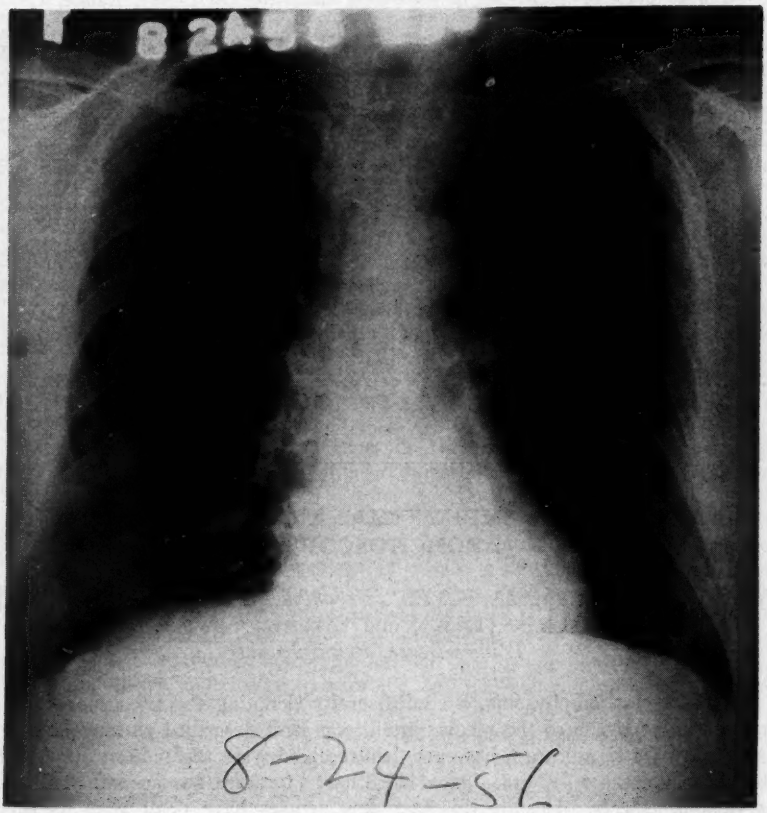

FIG. 1. Postero-anterior roentgenogram in inspiration, showing first stage anthracosilicosis and a possible mass in the left hilar region (August 24, 1956).

of a main airway may be responsible for the complicating "mediastinal," "pulmonary interstitial" and "subcutaneous" emphysema.

CASE REPORT

The patient was a 60 year old white male, a retired miner and foundry worker who had been employed in these occupations for approximately 15 years. His first admission was on April 22, 1956, for chronic bronchitis and pulmonary emphysema. At that time his chief complaints had been: (1) progressive exertional dyspnea of

about five years' duration, and (2) nonseasonal periodic wheezing, occurring at rest but more pronounced after exertion. The physical examination had not been remarkable except for an increase in the anteroposterior diameter of the chest and the presence of expiratory rhonchi throughout both lung fields. In view of his occupational history, the x-ray of the chest had been interpreted as first-stage anthracosilicosis. Pulmonary ventilatory tests had disclosed impairment of ventilation, obstructive in type, attributed to the bronchitis and the pulmonary emphysema. The remainder of

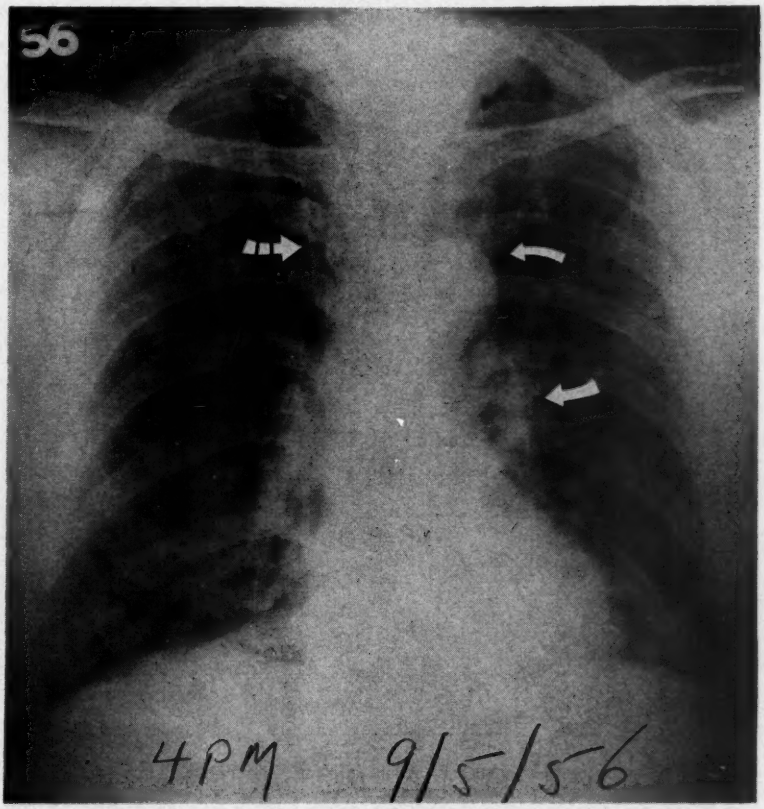

FIG. 2. Postero-anterior roentgenogram in inspiration, showing bilateral displacement of the mediastinal pleurae, air in the lateral chest walls and neck, and bilateral air streaks in the pulmonary fields indicative of air either in the anterior and posterior chest walls or in the chest walls and pulmonary interstitial tissue (4 p.m., September 5, 1956).

the laboratory data had not been remarkable. On therapy with bronchodilators and potassium iodide the bronchitic symptoms had subsided and the patient had been discharged on May 3, 1956.

His second and current admission was on August 22, 1956, with complaints similar to those mentioned above. Physical examination on admission revealed a well developed, well nourished 60 year old white male in no distress. Except for increased anteroposterior diameter of the chest and expiratory rhonchi, as noted previously, the

physical examination was not remarkable. Urine analysis was normal; complete blood count, normal; blood VDRL (Venereal Disease Research Laboratory), negative; blood urea nitrogen and blood sugar, normal. X-ray of the chest on August 24, 1956 (figure 1), again disclosed first-stage anthracosilicosis and, in addition, a possible mass in the left hilar region. The electrocardiogram was normal. Because of the x-ray suggestion of the possibility of a bronchial tumor on the left, a diagnostic bronchoscopy was performed on September 5, 1956, at approximately 8:00 a.m. The patient returned from the operating room at 9:45 a.m. in no distress. The bronchoscopic findings were reported as normal except for a small elevation of the mucosa at the

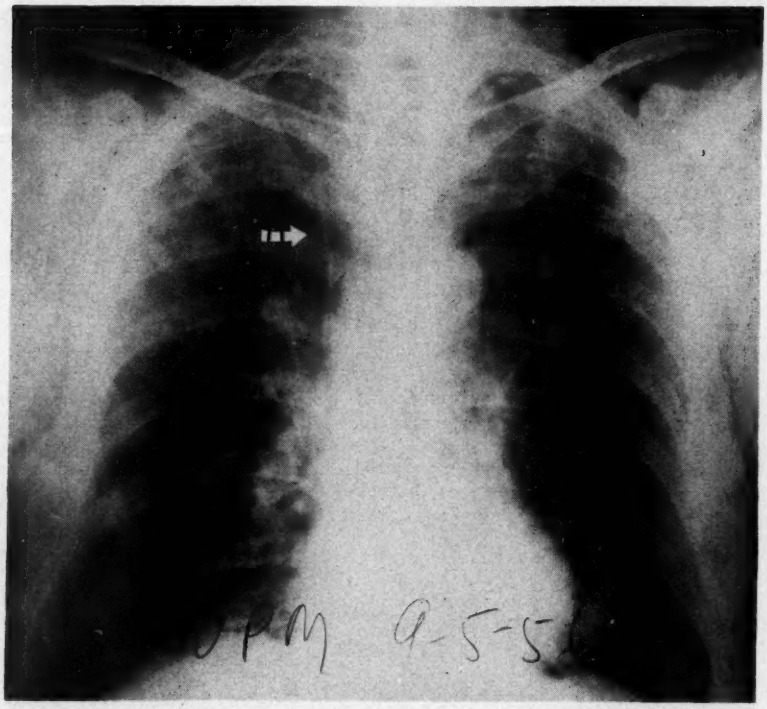

FIG. 3. Postero-anterior roentgenogram in inspiration, the immediate postoperative film showing displacement of the mediastinal pleura on the right only, air in the lateral chest walls and neck, and air streaks only in the left pulmonary field, indicative of either chest wall emphysema or pulmonary interstitial emphysema (10 p.m., September 5, 1956).

junction of the left main bronchus and the left upper lobe bronchus. A biopsy was taken at this site and material was aspirated from the left main bronchus for microscopic examination. Neither the biopsy nor the aspirated material disclosed any evidence of malignancy. The biopsy specimen was reported to show chronic bronchitis and the presence of muscle tissue and mucous glands. At 12:35 p.m., about three hours after the bronchoscopy, marked subcutaneous emphysema involving the neck, face, chest and arms was noted. At this time the patient did not manifest any respiratory distress, and examination of the heart revealed no unusual findings. Hamman's sign [1] (peculiar sounds consisting of crackles, bubbles or crunches present

during systole, or during systole and diastole) was not audible at this time or subsequently. The lungs, however, still revealed expiratory wheezes. At 4:00 p.m. the subcutaneous emphysema had extended to the forearms and the eyelids, the eyes were practically closed, and the subcutaneous emphysema of the neck and chest was more pronounced. Other than mild substernal pain and the discomfort caused by the subcutaneous emphysema, the patient had no complaints. X-ray of the chest taken at 4:00 p.m. (figure 2) disclosed not only subcutaneous emphysema in the neck and lateral chest walls but also mediastinal emphysema. It also showed subcutaneous

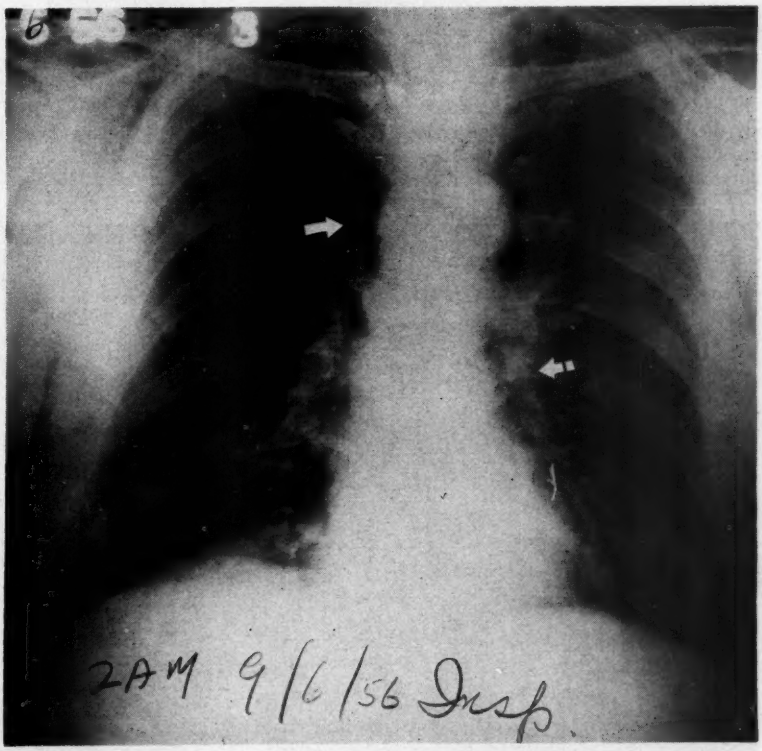

FIG. 4. Postero-anterior roentgenogram in inspiration, showing bilateral displacement of the mediastinal pleurae and subcutaneous emphysema. No air streaks are seen in the pulmonary fields (2 a.m., September 6, 1956).

emphysema of the anterior and posterior chest walls and possible pulmonary interstitial emphysema. The latter possibility was suggested by the presence of "air streaks" through both pulmonary fields radiating from the hilum to the periphery. At 6:00 p.m. on the same day the patient was cyanotic and quite dyspneic, and complained of marked substernal pain. Tachycardia and a moderate fall in blood pressure were noted. The electrocardiogram at this time disclosed minor ST-T segment abnormalities. Although he received sedatives, oxygen by mask, and intravenous aminophylline, he experienced no relief from the respiratory embarrassment, which was manifested by splinting of the chest in inspiration and marked wheezing on ex-

piration. His condition failed to improve and an emergency operation was performed at 9:00 p.m. A horizontal incision, about 3.5 inches long, was made in the subcutaneous tissue of the neck just above the sternum and the clavicles, and an artery forceps was inserted into the mediastinum and spread open. As a result of these maneuvers, air escaped from both the subcutaneous tissue and the mediastinum, and the patient experienced marked relief from his respiratory difficulty and substernal pain. A soft rubber drain was then inserted into the mediastinum and the surgical incision was loosely closed by sutures. The patient received oxygen by nasal catheter during the entire procedure. After the operation he was placed on tetracycline and streptomycin. At 10:00 a.m., approximately 20 minutes after the operation, an x-ray of the chest (figure 3) again disclosed subcutaneous emphysema of the neck and the lateral chest walls. Air, however, was present only on the right side of the mediastinum, and no air was present in the pulmonary fields, the air streaks having disappeared. At approximately 1:30 a.m. on September 6, 1956, despite the continuation of nasal oxygen, moderate dyspnea was again observed. X-rays of the chest on both inspiration and expiration were taken at 2:00 a.m. The inspiratory film (figure 4) disclosed the presence of air not only on the right side but

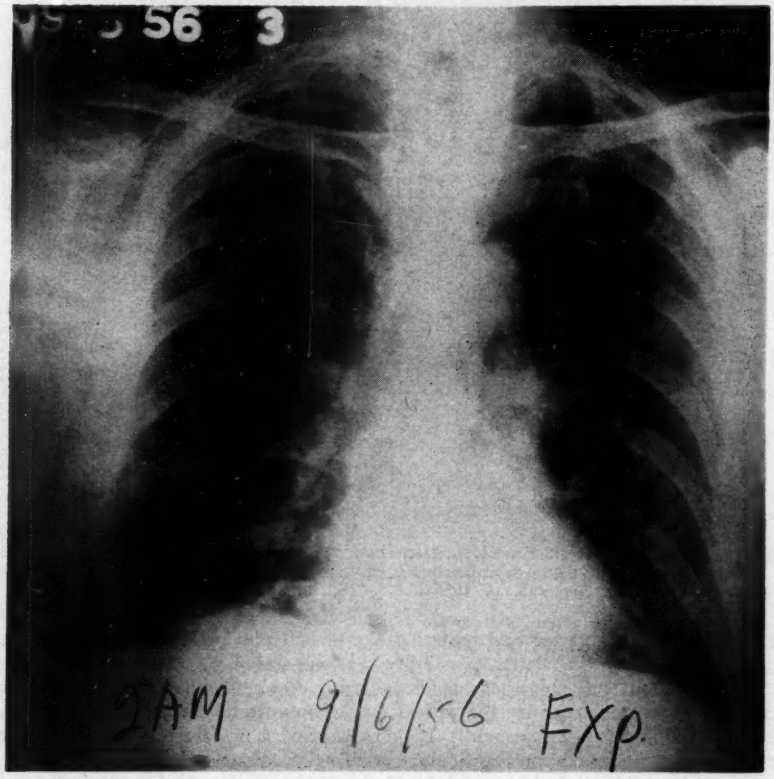

FIG. 5. Postero-anterior roentgenogram in expiration, showing, in comparison with figure 4, the disappearance of the mediastinal pleurae and the appearance of air streaks in the left pulmonary field (2 a.m., September 6, 1956).

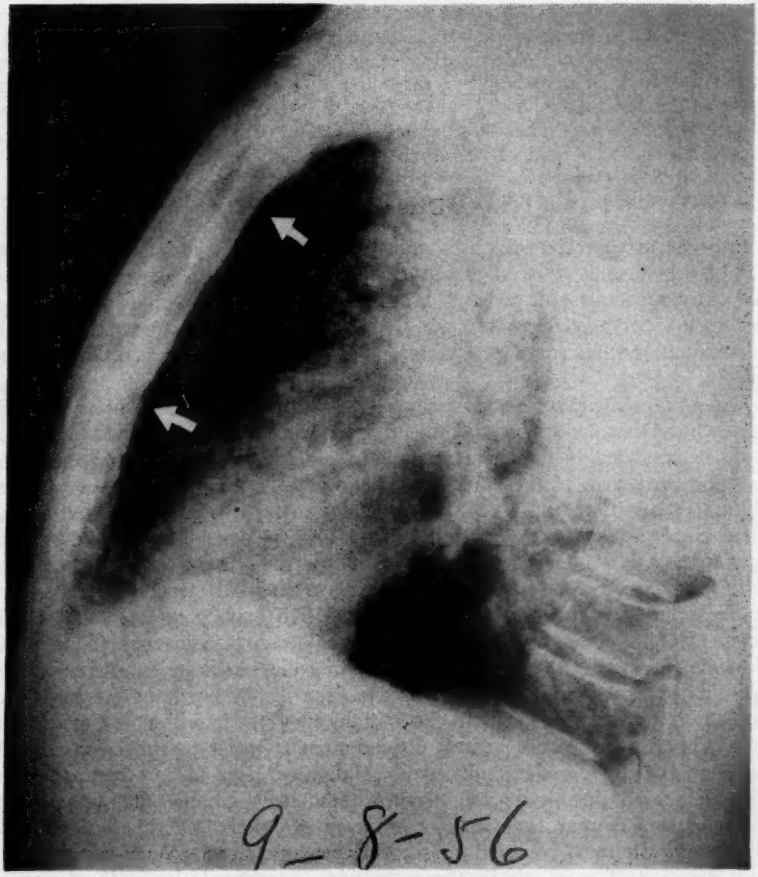

FIG. 6. Lateral roentgenogram, showing a thin layer of air beneath the sternum (September 8, 1956).

also on the left side of the mediastinum. The expiratory film (figure 5) failed to show any air in the mediastinum, but disclosed the probable presence of air in the pulmonary interstitial tissue and/or in the subcutaneous tissue of the chest wall on the left, manifested by the air streaks radiating from the hilum. With oxygen, antibiotics, aminophylline and intravenous hydrocortisone, the dyspnea disappeared by the afternoon of September 6, 1956. From this time on the patient had no further respiratory distress and the oxygen therapy was terminated. The hydrocortisone was also discontinued, but intramuscular ACTH was administered on September 7 and 8, 1956. The antibiotics were discontinued on September 11, 1956. The drain was also removed on this date. The tachycardia and the fall in blood pressure disappeared by September 10. The patient had a low grade fever for two days only—September 6 and 7—the temperature curve being normal before and after these dates. A postero-anterior x-ray of the chest on September 8 (not shown) disclosed only subcutaneous emphysema of the lateral chest wall and neck, without evidence of

mediastinal or pulmonary interstitial emphysema. A lateral chest film of the same date (September 8, figure 6), however, disclosed a thin layer of air in the mediastinum just beneath the sternum. By September 17 the subcutaneous emphysema of the chest, neck, face and upper extremities had completely vanished. Both the postero-anterior and lateral x-rays of the chest were completely normal by September 18 except for first-stage anthracosilicosis. The electrocardiogram on September 20 was also normal. The patient was discharged on October 4, 1956.

Discussion

In order to appreciate the mechanism which might have led to the development of the various types of emphysema in this patient, a short discussion of some of the aspects of this problem will be presented at this point. We will consider such aspects as diagnosis, pathways of air entry into and exit from the mediastinum, mechanism of production, pathologic physiology, classification and therapy.

Diagnosis: Since substernal pain is a prominent symptom of mediastinal emphysema, other conditions prominently characterized by pain at the same site should be included in its differential diagnosis, such as myocardial infarction, dissecting aneurysm of the aorta, acute pericarditis, and spontaneous pneumothorax. In addition, rupture of the esophagus, which might cause both mediastinal emphysema and mediastinitis, must also be considered. The presence of air in the subcutaneous tissue of the neck and the postero-anterior erect chest film is a characteristic feature if an air leak from local structures in the neck can be excluded. The postero-anterior chest film usually discloses lateral displacement of the mediastinal pleura of each side and radiolucency of air within the mediastinum.[5] The lateral chest film is not diagnostic unless pneumothorax is eliminated as a possibility. In our case, the displacement of the pleura appears to be more prominent than the radiolucency of air within the mediastinal space. This is so because pleural displacement is easier to recognize than the change in the degree of radiolucency. Hamman's sign is not pathognomonic unless left-sided pneumothorax, marked pulmonary emphysema, pneumoperitoneum, and a dilated esophagus or stomach are excluded.[6] Left-sided pneumothorax is the most common cause of Hamman's sign.[6] With regard to the x-ray demonstration of air in the pulmonary interstitial tissue, there are apparently somewhat diverse opinions. Cocchi [7] states that pulmonary interstitial emphysema cannot be demonstrated by x-ray. On the other hand, Rabin [8] and Rubin [9] believe that this might be possible in some instances. Rabin suggests that x-ray diagnosis of pulmonary interstitial emphysema may be justified when "persistent aeration" is noted in the expiratory film along with "diminished elevation of the diaphragm"; while Rubin explains that the presence of radiating "air streaks" within the pulmonary fields "in some instances" might suggest pulmonary interstitial emphysema.

The difference in the views of Cocchi and Rabin might possibly have arisen from the fact that Cocchi may have been considering inspiratory films *only*, while Rabin's suggestion depends upon a comparison of inspiratory and expiratory films. Normally, in the expiratory film the pulmonary fields are not so radiolucent as in the inspiratory film, and the leaves of the diaphragm are higher. It is suggested, therefore, that a diagnosis of pulmonary interstitial emphysema may be justified by x-ray examination when the pulmonary fields in the expira-

tory film are as radiolucent as in the inspiratory film and the leaves of the diaphragm are as low as in the inspiratory film. In other words, when this contrast in radiolucency is lost between the expiratory and the inspiratory films the presence of pulmonary interstitial emphysema may be suggested. In our experience this comparison is not so easy as it may sound, and at best the adequate recognition of different shades of radiolucency is far from satisfactory. As for the presence of radiating air streaks in the pulmonary fields as a diagnostic feature of pulmonary interstitial emphysema, it is apparent that these lend themselves to easier visual recognition. We would like, however, to stress the point that the presence of these radiating air streaks might just as well indicate the presence of subcutaneous emphysema in the anterior or the posterior or both chest walls. The differentiation by x-ray between air in the subcutaneous tissue of the chest wall and air in the pulmonary interstitial tissue could prove to be very difficult, and when air is present in both of these spaces at the same time the differentiation might become practically impossible. In our opinion, this situation is further complicated by what we believe to be a fact—that extensive subcutaneous emphysema following mediastinal emphysema is probably always accompanied by pulmonary interstitial emphysema. From the inspiratory and expiratory films of the chest shown in figures 4 and 5, it is evident that there is air in the mediastinum during inspiration, whereas none is apparently present during expiration. It would appear, therefore, that during inspiration air enters the mediastinum and the pulmonary interstitial tissue, where the pressure is lower than in the pulmonary alveoli,[10] while during expiration it is expelled into the subcutaneous tissues. The pressure changes in these various spaces during inspiration and expiration appear to influence the presence of air in one space or the other. During inspiration, pressure is higher in the pulmonary alveoli than it is in the mediastinum and the pulmonary interstitial spaces. During this phase of respiration, air is being forced into the alveoli under atmospheric pressure. At the same time, in the presence of an "air-leak" (as in this case presented), and because of the difference of pressure gradients, air will move from the alveoli into the mediastinum and into the pulmonary interstitial tissue. Thus, air will be present in both the alveoli and the pulmonary interstitial spaces, and there will therefore be no "contrast" between the two spaces, and thus the air streaks will be absent or at least less prominent on the inspiratory film. During expiration the pressure is higher in the mediastinum, just as it is in the pleural cavity, but not so high as the pressure in the pulmonary alveoli. During this phase of respiration, air is forced out of the alveoli, thus leaving the alveolar bed partially empty. Although part of this alveolar air is forced out of the body through the airways, another part of it is forced into the pulmonary interstitial space and into the mediastinum because of the presence of the air leak. No air is noted in the mediastinum, however, in the postero-anterior view of the expiratory film because during this phase of expiration the air is forced away from the mediastinum, probably into the subcutaneous tissue. We therefore have here a situation in which there is air in the pulmonary interstitial tissue but no air or a decreased amount of air in the alveoli. This situation produces a "contrast" on the film and air streaks are therefore noted on the expiratory film. In this latter situation, however, these air streaks might represent air in either the pulmonary interstitial tissue or the subcutaneous tissue of the chest wall, or both. We believe an absolute dif-

ferentiation is not possible. Our experience, however, encourages us to attempt an x-ray diagnosis to this extent, that (1) if air streaks are present in the inspiratory film, air is probably present in the subcutaneous tissue, with or without air in the pulmonary interstitial tissue; and (2) if air streaks are not seen in the inspiratory film but are present in the expiratory film, air is probably present in the pulmonary interstitial tissue. A more positive attitude than this does not seem to be justifiable. The electrocardiogram shows no characteristic findings to be diagnostic. In our case, minor nonspecific ST-T segment changes were noted.

Pathways of Air[1, 11, 12]: Air may reach the mediastinum from the interstitial tissue of the lungs and from air-bearing structures of the mediastinum itself. It may both reach and escape from the mediastinum along the retroperitoneal tissues, where it can be detected by x-ray examination, and the subcutaneous tissues of the neck, where it can be easily found by physical examination. Air escaping from the mediastinum into these areas is undoubtedly beneficial to the patient, since the pressure in the mediastinum is lowered. Unfortunately, it may also escape by infiltrating the interstitial tissues of the lungs, and may produce pneumothorax by rupturing the pleural membranes. Air in these sites, as well as in the mediastinum, may be of serious consequence to the patient.

Mechanisms of Production[1, 11, 12, 13, 14, 15]: The causes of mediastinal emphysema appear to be legion. They may be nontraumatic or traumatic (including diagnostic and operative procedures). The source may be above or below the diaphragm. To mention just a few: penetrating wounds of the maxillary sinus and of the trachea in the neck and following tracheotomy; traumatic perforation of the trachea or main bronchus in the mediastinum; rupture of a hollow abdominal viscus with release of air in the retroperitoneal tissues; and following perirenal insufflation of air and pneumoperitoneum. However, the rupture of apparently normal or overinflated alveoli into the pulmonary interstitial tissues is probably the most common cause of mediastinal emphysema. Macklin[12] believes that pulmonary alveoli may rupture under normal or increased pressure. This kind of rupture is sometimes noted to occur without evident cause and is termed "spontaneous." It might occur as a result of increased expiratory pressure. This latter might occur during childbirth, improperly administered anesthesia, or such severe strain as excessive cough, asthmatic attacks, and blowing against obstruction.

In our patient, we believe one of the following three mechanisms might have produced the mediastinal emphysema: (1) direct perforation of the trachea or the main bronchus by the bronchoscope; (2) perforation of the left main bronchus by the biopsy forceps; (3) the rupture of emphysematous alveoli incidental to the increased expiratory pressure produced by the presence of the bronchoscope in a patient who already had demonstrated obstructive ventilatory signs prior to bronchoscopy.

Considering these three different mechanisms one by one as possible causes in the production of the mediastinal emphysema in the above reported case, one could probably eliminate the first, since the bronchoscope was passed without difficulty. The operator was certain that neither the trachea nor the bronchus was perforated by the instrument. It is more plausible to believe that either the second or the third mechanism was operative in this case. The presence

of the air streaks only on the left side in figures 3 and 5 affords further evidence to support the probability of mechanism No. 2 (traumatic perforation during the biopsy procedure), since the biopsy was taken on the left side. Although the mechanical manipulation involved in the biopsy procedure appears to be the more likely mechanism under the circumstances, we would nevertheless like to stress the hypothesis that mechanism No. 3 is a possibility. The validity of this theory is supported by Comroe's view,[16] that additional airway resistance is imposed by the insertion of a long, narrow instrument such as a bronchoscope into the pulmonary airways. Also, with regard to this particular mechanism, if one assumes that increased expiratory pressure in association with pulmonary emphysema is the primary factor involved, then pneumothorax may be expected to develop as a complication of bronchoscopy in patients with localized or generalized pulmonary emphysema. This must be so since, with the production of interstitial pulmonary emphysema, air may dissect not only the mediastinum, causing mediastinal emphysema, but may also dissect and cause rupture of the visceral pleura and produce a pneumothorax. A search of the literature discloses at least two such reports [17, 18] in which pneumothorax was a complication of bronchoscopy. In the first of these reports, dealing with four patients, three had conditions in which pulmonary emphysema, localized or general, was probably a part of the picture. In the second report, dealing with one patient who had a bronchogenic tumor, pneumothorax also developed and was located on the same side as the tumor. Consideration of this mechanism as a cause of mediastinal emphysema leads one to believe that the incidence of this complication is higher in patients with pulmonary emphysema than has been recognized or reported. This may also be true with regard to pneumothorax as a complication of bronchoscopy. We therefore believe that bronchoscopy is a distinct danger to the patient with pulmonary emphysema, in that it may be complicated by mediastinal emphysema or pneumothorax. With this in mind, it is suggested that x-rays of the chest taken after bronchoscopic procedures may help to reveal the increased incidence of these complications. Lateral chest x-rays might be more helpful in making an earlier diagnosis.

Classification

On the basis of whether or not cardiorespiratory embarrassment is present, mediastinal emphysema is classified as malignant or benign.[6, 11, 12, 13] In the benign form, the pressure disturbance in the mediastinum resulting from the intrusion of air is minimal. This is so because either the air has entered the mediastinum only in small amounts or, if it has entered in large amounts, it has escaped into the subcutaneous tissues of the body, thus lowering the mediastinal pressure to relatively normal levels. In the malignant form, cardiorespiratory embarrassment occurs chiefly because of the increased mediastinal pressure and the extensive infiltration of the air through the pulmonary interstitial tissues. A complicating pneumothorax, if present, adds to the distress. As a result, there are displacement and limited motion of the lungs, restriction of the blood flow through the vena cava and the pulmonary veins and hypoxia, with resultant pulmonary arterial constriction and hypertension.[1, 6, 12] In our patient, the signs of cardiorespiratory embarrassment were fairly severe and were manifested by splinting of the lungs, tachycardia, fall in blood pressure, dyspnea and cyanosis.

If such embarrassment had not been corrected by draining the air from the mediastinum, a fatal outcome could have been conceivable.

Therapy

The therapy of mediastinal emphysema depends upon whether it is malignant or benign. The benign form requires no specific therapy. The malignant form requires urgent surgical intervention such as described in our case, followed by administration of oxygen, sedatives, antibiotics, bronchodilators, and steroid and ACTH therapy. It is important to emphasize the fact that the benign type may become malignant if an unfavorable disproportion develops between the entry of air into and escape of air from the mediastinum; therefore, even the benign form demands close clinical scrutiny.[19] In addition to the drainage of air by subcutaneous incisions in the neck, Lindskog and Liebow [20] recommend tracheotomy for several reasons. They believe that, by by-passing the glottis, this procedure avoids the possibility of building up further pressure in the mediastinum during cough and strain, and also allows insertion of a suction catheter to aspirate blood and secretions. These same authors recommend aspiration of air by a needle through parasternal spaces in infants with malignant mediastinal emphysema, hoping to avoid surgical drainage by incision. It also occurs to us that in a patient with pneumothorax and mediastinal emphysema combined, the drainage of the pneumothorax might be one means of draining the air from the mediastinum. It cannot be too strongly emphasized that early diagnosis and early intervention are indispensable if one has to avoid the dangers inherent in malignant mediastinal emphysema.

Summary

1. On the basis of the presence or absence of cardiorespiratory embarrassment, mediastinal emphysema may be classified as malignant or benign. The benign type may become malignant. Prompt surgical intervention might be a life-saving measure in the malignant type.

2. A case is reported where a patient with chronic bronchitis and pulmonary emphysema developed mediastinal emphysema as a complication of bronchoscopy. It proved to be of the malignant type. Therapy was both surgical and medical, the latter consisting of oxygen, sedatives, antibiotics, bronchodilators, and adrenal cortical steroids and ACTH.

3. The possible mechanisms of the production of mediastinal emphysema are discussed. Though perforation of the airways by the bronchoscope itself was considered as one of the possible causes in this case, it is believed to be improbable. A perforation of the left main bronchus by the biopsy forceps was more likely the cause. Another possible mechanism was presented and discussed. This latter assumes the rupture of emphysematous alveoli of the lungs incidental to the increased expiratory pressure produced by the presence of the bronchoscope in the airways. This mechanism is considered to be more likely in patients who demonstrate signs of obstructive ventilation. If it is assumed that this particular mechanism can cause mediastinal emphysema, then bronchoscopy should be considered a distinct hazard in patients with pulmonary emphysema. It is suggested that the incidence of this complication of bronchoscopy may be higher in the emphysematous patient than has been generally recognized. Chest

x-rays taken soon after bronchoscopy may help to show air in the mediastinum which might ordinarily have been unrecognized.

4. The postero-anterior chest film, along with the lateral chest film, should reveal the presence of mediastinal emphysema. It is suggested that a postero-anterior expiratory film showing air streaks locally in the pulmonary fields may be diagnostic of pulmonary interstitial emphysema.

5. It is also suggested that when pulmonary interstitial emphysema and subcutaneous emphysema are present at the same time, it may be impossible to distinguish between the two. In our opinion, when mediastinal emphysema is present in its malignant form, one should also expect the presence of both pulmonary interstitial and subcutaneous emphysema.

ACKNOWLEDGMENT

We wish to acknowledge the assistance of the Chief Librarian, Mrs. Claire Tedesco, the Medical Librarian, Miss Louise Geroulo, and Miss Mary Burke, Secretary, Medical Service, in the preparation of the bibliography and the manuscript, and wish to thank them for their effort.

SUMMARIO IN INTERLINGUA

Emphysema mediastinal denota le presentia de aere in le histos conjunctive del mediastino. Secundo que embarasso cardiorespiratori es presente o absente, illo es classificate como maligne o benigne. Le embarasso cardiorespiratori in le typo maligne occurre principalmente como resultato de un marcate augmento del pression mediastinal e de un extense infiltration de aere a transverso le histos interstitial pulmonar. Le complication de pneumothorace pote augmentar le embarasso. Le typo benigne, in que le pression mediastinal non es augmentate significativemente, non require un therapia specific. Le typo maligne require le prompte intervention chirurgic como mesura de salva-vita.

Dolores substernal es un symptoma prominente de emphysema mediastinal del typo maligne. In le examine physic le presentia de emphysema subcutanee del collo es probabilemente diagnostic, si escappamento ab le structuras aerifere in le collo es eliminate. Un tracto characteristic in le diagnose roentgenologic de emphysema mediastinal es le presentia, in le roentgenogramma thoracic postero-anterior, de duo lineas opac paramediastinal, un a cata latere del linea central, indicante displaciamento del pleuras mediastinal per aere intra le mediastino. In ille roentgenogramma, le aere mediastinal non es necessarimente plus radiolucente que le aere in le adjacente campos pulmonar. In altere parolas, le diagnose roentgenologic de emphysema mediastinal depende quasi exclusivemente del recognition del lineas paramediastinal.

Es reportate le caso de un patiente con chronic bronchitis e emphysema pulmonar, sub suspicion de haber un malignitate bronchogenic, qui disveloppava maligne emphysema mediastinal, subcutanee, e pulmono-interstitial post bronchoscopia e biopsia de un micre tumescentia del broncho sinistro-major. Studios histologic del specimen produceva nulle evidentia de malignitate. Le therapia, consistente de drainage of chirurgic del mediastino, sequite per inhalation de oxygeno, antibioticos, bronchodilatatores, e steroides, resultava in un complete restablimento.

Ben que, in le caso reportate, le mechanismo per que le emphysema mediastinal esseva effectuate esseva probabilemente le perforation de un broncho major per le forcipe bioptic e non per le bronchoscopio mesme, il pare possibile postular un altere mechanismo sin participation de trauma. Iste mechanismo presume le ruptura de alveolos emphysematose a in le histo pulmono-interstitial, con dissection de aere a in le mediastino, in consequentia del summation de augmentos del pression in le vias expiratori (causate per bronchitis chronic e emphysema pulmonar) e del augmento

de pression in le vias expiratori (causate per le presentia del bronchoscopio mesme). Si on accepta le possibilitate que iste mechanismo pote causar emphysema mediastinal e/o pneumothorace, il seque que bronchoscopia debe esser considerate como un hasardo definite in patientes con bronchitis chronic e/o emphysema pulmonar. Es formulate le opinion que le incidentia de tal complicationes es possibilemente plus alte que lo que es generalmente recognoscite. Le validitate de iste supposition pote esser determinate per le effectuation de roentgenogrammas thoracic tosto post le manovra bronchoscopic. Roentgenogrammas in le caso reportate demonstra non solmente emphysema mediastinal e subcutanee sed etiam un probabilemente localisate emphysema pulmono-interstitial in le vicinitate del sito del biopsia.

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MASSIVE DILATATION OF THE LEFT ATRIUM: A CASE REPORT *

By Morris A. Shapiro, M.D., F.A.C.P., and Gerald W. Parker, M.D.,
Schenectady, N. Y.

Moderate enlargement of the left atrium in mitral stenosis is not an unusual finding, but massive dilatation is considered a rare entity. Since Owen and Fenton [1] described the first case of massive dilatation in 1901, fewer than 40 cases have been reported.

The following case history is presented because it illustrates the progressive enlargement of the left atrium resulting in massive dilatation. The course of the disease was observed with x-rays and physical examinations over an interval of 12 years.

Case Report

A 24 year old white male was first seen at Ellis Hospital on September 30, 1943, with the chief complaints of shortness of breath, swelling of the ankles and expectoration of blood. At the age of 13 he had had scarlet fever, and at 18 had been told that he had a murmur. He was employed as a laborer, and had experienced no distress until three weeks before admission, when he became short of breath on exertion. He soon became unable to work, and on two occasions expectorated red, frothy sputum. He became restless at night and found himself unable to walk in comfort.

Physical examination revealed a poorly nourished white male in moderate distress. Blood pressure, 140/90 mm. of Hg; pulse, 112; respiration, 28; temperature, 105.4° F. The patient was sitting upright in bed and was tachypneic at rest. Head, eyes, ears, nose and throat were not abnormal. The neck veins were moderately congested but no pulsations were noted. The thorax was kyphotic, and a systolic heave was apparent. The lungs exhibited no dullness to percussion, but auscultation revealed fine moist râles at the bases bilaterally. There was some diminution of breath sounds in the right chest posteriorly to the level of the right scapula. The heart was enlarged to the left and downward to the anterior axillary line; no thrill was palpable. Auscultation revealed a grade 2 systolic murmur at the apex, transmitted to the left axilla; rate, 112. Cardiac rhythm was irregular and unequal, with a pulse deficit. The second pulmonic sound was greater than the second aortic. The abdomen revealed the liver to be five fingerbreadths below the right costal margin; it was tender but did not pulsate. There were no masses. The spleen and kidneys were not palpable, and no ascites was present. Rectal examination elicited no abnormal findings. Genitalia were normal. Three plus pitting edema of the ankles and pretibial regions was present. Neurologic examination was negative. Laboratory data were: hemoglobin, 10.8 gm.; white blood cells, 19,000; blood urea nitrogen, 11; serologic test for syphilis, negative. Urinalysis: specific gravity, 1.012; albumin, very faint trace; sugar, absent. Sputum revealed pneumococcus by Neufeld's method, but no typing was carried out. Chest x-ray showed a marked enlargement of the heart, with special fullness of the outflow tract of the right ventricle and increased density in the region of the left auricle. The hila were considerably increased in density, suggesting pulmonary congestion (figure 1). An electrocardiogram revealed auricular fibrillation.

* Received for publication August 15, 1956.
From the Department of Medicine, Ellis Hospital, Schenectady, N. Y.
Requests for reprints should be addressed to Morris A. Shapiro, M.D., 1603 Union Street, Schenectady 8, N. Y.

The patient was considered to have rheumatic heart disease (inactive), mitral stenosis, atrial fibrillation, congestive failure, and right lower lobe pneumonia. He responded well to oxygen, digitalis, bed-rest and aminophylline, and was discharged after 17 hospital days.

In May, 1944, the patient was readmitted complaining of cough, fever, chills and shortness of breath. He had had a respiratory infection for about two weeks, and

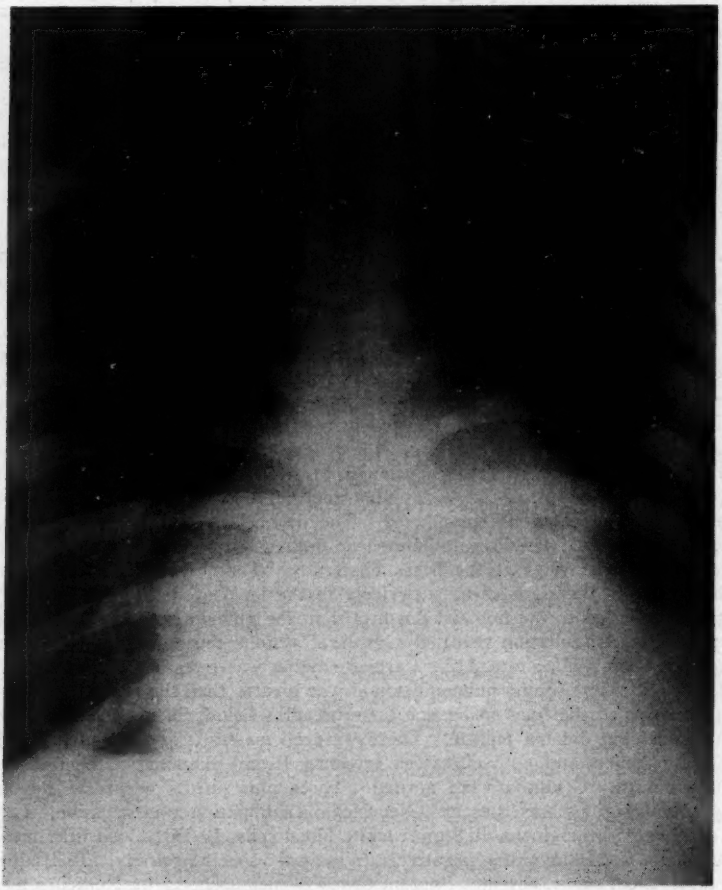

FIG. 1. Portable roentgenogram taken October 2, 1943, revealing marked left auricular enlargement and enlargement of right ventricle.

two days prior to admission developed malaise, chills and fever. He had been taking digitalis regularly since his previous admission but had discontinued its use one month prior to admission because he "felt so much better." On the morning of admission the patient stated he had coughed up bright red blood. Examination revealed him to be acutely ill, coughing frequently and mildly cyanotic. Temperature, 102.6° F.; pulse, 97; respiration, 24; blood pressure, 120/82 mm. of Hg. Skin was

dry and hot but had no rash or purpuric areas. The alae nasae were distended and flaring with each respiration; the nasopharynx was injected. There was no dullness of the chest, but numerous coarse râles were heard throughout, and a pleural friction rub was evident at the apex. The heart was enlarged to the extent described on the first admission, the rate was totally irregular, and a grade 3 systolic murmur

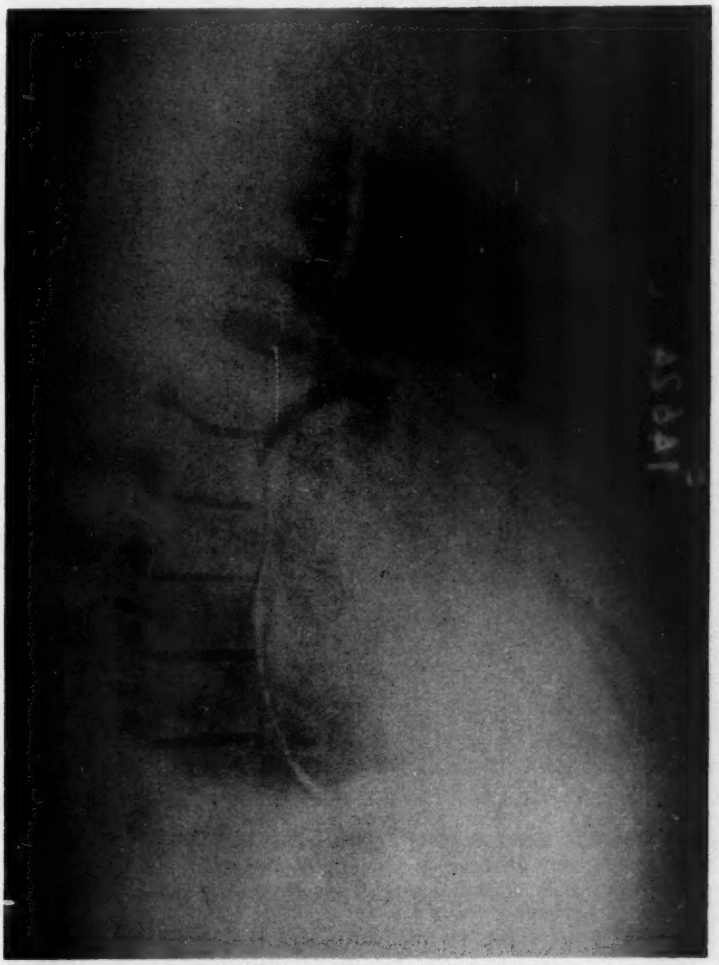

FIG. 2. Roentgenogram taken July 26, 1948, showing lateral view of enlarged left auricle, relatively unchanged since 1943.

was heard at the apex. The extremities revealed 3 plus pitting edema; Homans' sign was not elicited. X-ray of the chest revealed that the heart silhouette had not changed markedly from the first admission, but pulmonary congestion of the right lower lung field was quite evident. The patient was considered to have broncho-

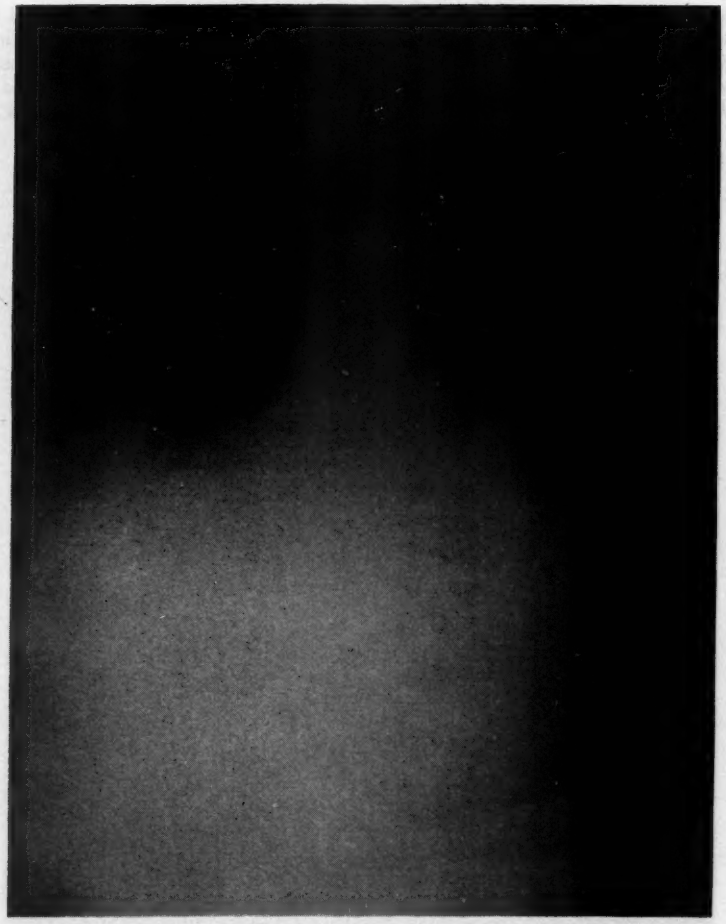

FIG. 3. Roentgenogram taken January 7, 1955, revealing considerable enlargement of heart since June, 1948.

pneumonia complicating the congestive failure of rheumatic heart disease. He was treated with sulfadiazine, digitalis, bed-rest and oxygen; he responded well and was discharged after 11 hospital days.

In June, 1948, the patient was readmitted with dyspnea, orthopnea, ankle edema and a cough of six weeks' duration. He had discontinued digitalis six weeks previously because he felt improved. Examination revealed him to be orthopneic, cyanotic about the lips and nailbeds, and coughing considerably. Lungs revealed dullness of the right base posteriorly, and moist, crepitant râles were heard in both bases. The heart rate was irregular and a pulse deficit was evident. The heart was enlarged to the anterior axillary line, a loud, blowing systolic murmur was present, and an aortic systolic murmur was also present which could not clearly be differentiated from the apical murmur. The liver was three fingerbreadths below the right costal

margin, and 4 plus pitting edema of the lower extremities extended to his knees. Chest x-ray revealed marked enlargement of the heart, affecting especially the left atrium. Bilateral hilar pulmonary congestion was present, and partial obliteration of the costophrenic angles gave evidence of slight pleural effusion bilaterally (figure 2). The electrocardiogram showed auricular fibrillation. On digitalis, bed-rest, aminophylline and diuretics the patient did well and was discharged after 11 hospital days.

In January, 1955, the patient was admitted for the fourth time. His complaints were shortness of breath, ankle edema, a burning sensation across his chest, difficulty in swallowing, and a feeling of discomfort and pressure in his chest. He had had

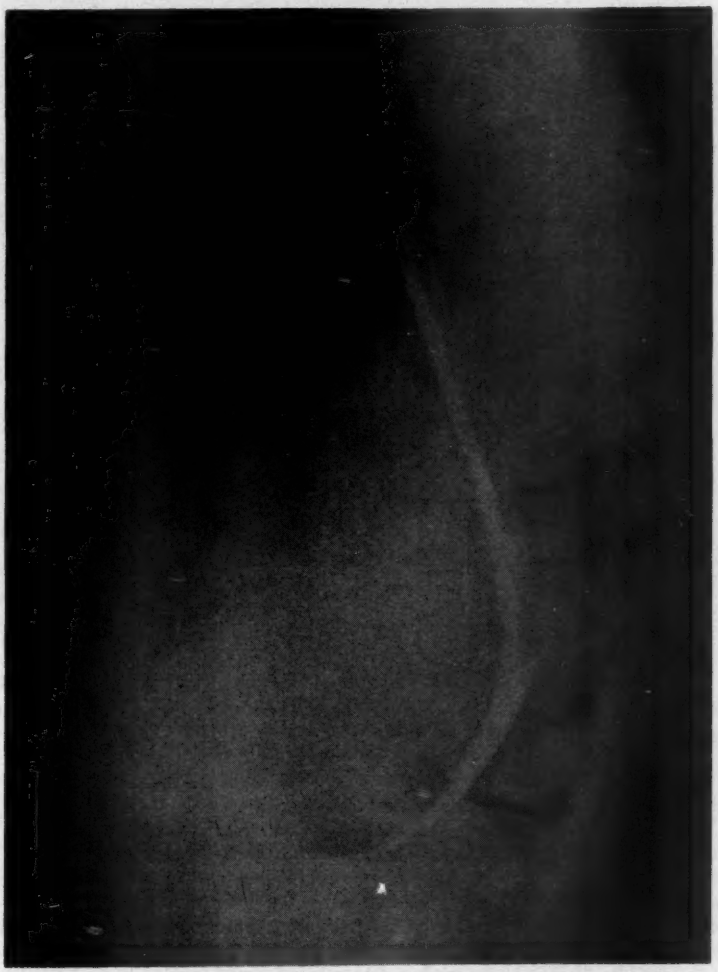

FIG. 4. Roentgenogram, lateral view, taken January 7, 1955, showing progressive marked enlargement of left auricle.

periodic bouts of severe shortness of breath since 1948, generally during or after exertion. In 1953 he had had a two- to three-day episode of hemoptysis which disappeared spontaneously. Chest x-ray revealed considerable enlargement in heart size since June, 1948. A large shadow in the chest, blending with and partially obscuring the heart, appeared from fluoroscopy to represent a large cystic mass. This was situated to the right and posterior to the heart, displacing the heart anteriorly and to the left. There was considerable pleural effusion on the right side, obliterating the costophrenic angle and extending to the level of the seventh rib when the patient was in an upright position. The esophagus was displaced to the right

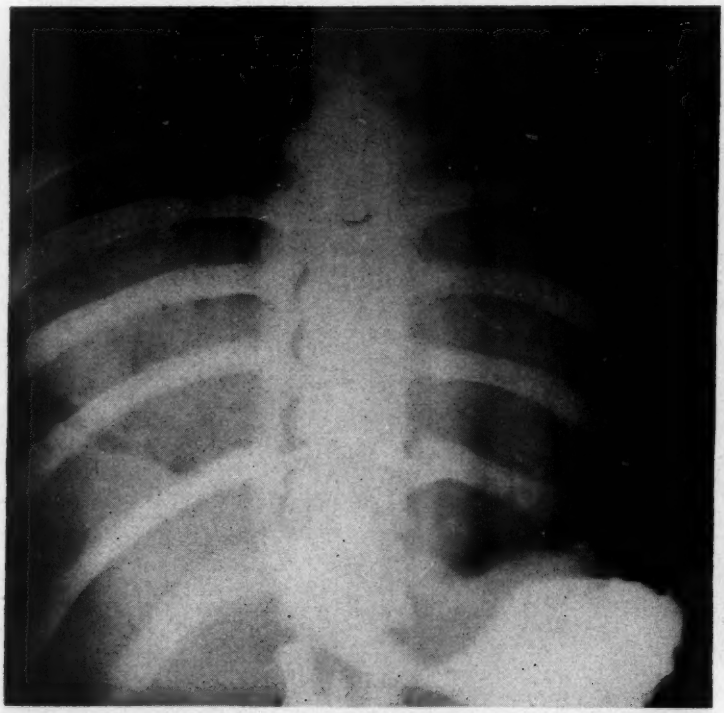

FIG. 5. Bucky film, revealing esophagus displaced to the right, due to marked left auricular enlargement (January 7, 1955).

and posteriorly (figures 4, 5 and 6). Comparison of the electrocardiogram with previous ones showed right ventricular strain and auricular fibrillation.

The patient left the hospital after 18 days and was followed in the clinic. He reëntered on February 3, 1955, complaining of nausea, vomiting and shortness of breath. The right pleural effusion had not diminished, and a thoracentesis was performed through the ninth right intercostal space in the midaxillary line. Four hundred cubic centimeters of clear amber fluid were removed. The patient withstood the procedure well and improved clinically.

On October 12, 1955, the patient was admitted with ankle edema, dyspnea and orthopnea of one week's duration. He had been lost to follow-up examinations since

February and had been taking digitalis sporadically. He had been in fair condition until one week prior to admission, when he rapidly developed ankle edema, orthopnea, dyspnea and anorexia. Examination revealed a chronically ill male, poorly nourished and in acute distress. Temperature, 99° F.; pulse, 108; respiration, 30; blood pressure, 120/90 mm. of Hg. Head, eyes, ears, nose and throat were not abnormal. The neck revealed that accessory muscles of respiration were being used. No marked venous congestion was present, and there was no nuchal rigidity. The thorax was kyphotic. Retractions on inspiration were evident. Dullness of the right base and lateral right chest was present. Bilateral fine crepitant râles were heard throughout except in the area of dullness posterolaterally on the right, where no breath sounds were heard. The heart was enlarged to the left, with the point of maximal impulse in the sixth left intercostal space in the anterior axillary line. A heaving thrust

FIG. 6. Photograph showing greatly dilated left auricle, extending posteriorly to the heart and projecting to the right with pericardium reflected.

was evident and a diastolic thrill palpable at the apex. Rate was 108 and irregular. P_2 was accentuated. Systolic and diastolic murmurs were heard over the precordium, but best at the apex. The abdomen was tense; the liver was three fingerbreadths below the right costal margin, and tender. Ankles and pretibial areas exhibited 3 plus pitting edema.

Laboratory Data: Hemoglobin, 13.1 gm.; white blood cells, 12,800, with 83 polymorphonuclears, 14 lymphocytes, 1 stab, 1 eosinophil and 1 monocyte. Urinalysis: specific gravity, 1.009; albumin and sugar, negative; white blood cells, 2 to 3 per high power field. Total protein, 6.0 gm. A/G ratio, 3.8/2.2. Sodium, 133; potassium, 4.9; chloride, 80; glucose, 133; blood urea nitrogen, 15; erythrocyte sedimentation rate, 32 mm./hr. Chest x-ray revealed no definite change in the size or contour of the heart since the admission in January, 1955. The pleural effusion on

the right had diminished slightly. An electrocardiogram revealed no significant change since tracings taken in January and February, 1955.

Therapy was begun and the patient seemed to be improving but died suddenly on his third hospital day.

Necropsy: The thorax was found to contain about 400 c.c. of pale yellow clear fluid in the right costophrenic sulcus. Bilateral pleural adhesions were present, but no fluid was found in the left hemithorax. A large cystic structure, located posterior to the heart, came around the right side of the heart and displaced the right lung in a cephalad direction so that the right middle lobe was completely atelectatic and the lower lobe was displaced out of the right costophrenic sulcus area in a cephalad direction. When dissected, the cystic structure was demonstrated to be the left atrium which after fixation measured 20 by 15 by 10 cm. and contained an estimated 1,500 to 2,000 c.c. of blood (figure 6). The myocardium was firm. The left ventricular wall measured 1.7 cm., the right, 0.8 cm. The mitral valve showed typical "fish-mouthing" when viewed from above. There were thickening, induration and rolling of the cusps (particularly of the anterior cusp) along their free edges. The aortic valve cusps showed fusion, thickening and stenosis of two of the cusps to produce the effect of a single cusp, thus making it, in effect, a two-cusp aortic valve. Valve measurements: aortic, 5.5 cm.; mitral, 8 cm.; pulmonic, 6.5 cm.; tricuspid, 12 cm.

Sections of the dilated left atrial wall showed focal thickening of the endocardium, with fibrous tissue replacement of the wall in some areas. There was marked interstitial fibrosis of the myocardium. No active Aschoff bodies were seen.

Discussion

According to Bedford,[2] extreme dilatation of the left atrium to the right has been associated in almost all cases with mitral stenosis, and often with adherent pericardium, which may be partial or complete. The latter is considered presumptive evidence of severe rheumatic carditis.[3] The finding of fibrotic changes in the myocardium of the left atrium is characteristic, and the etiology of the massive enlargement is inherently associated with thinning of the atrial wall as a result of increased intra-auricular pressure from stenosis and often an accompanying regurgitation.[4] Because the anatomic position of the left atrium is such that the left main stem bronchus is intimately in association superiorly, the esophagus and vertebral column posteriorly, and the left ventricle on the left, massive enlargement can take place only to the right. Nichols and Ostrum[5] mention that Bordet found the left atrium to the right, beyond the right atrium, in 5% of a large series of cases of mitral stenosis examined by roentgenologic methods.

In the earlier stages there are no characteristic physical signs, and only roentgenologic study makes the diagnosis possible. The x-ray examinations should be in the oblique positions, preferably the right anterior oblique, and should always include fluoroscopy and barium swallow. East[6] and Parkinson[7] feel that oblique x-ray examination is the most helpful single procedure in cases of obscure cardiac enlargement. When the enlargement is such that the right thoracic wall is reached by the enlarging atrium, certain signs are suggestive. Dullness may be present to the right of the sternum and in the right axilla, and a forcible systolic thrill may be palpable to the right of the sternum. This thrill may also be palpable in the right axilla at the fourth or fifth interspace, and a murmur will accompany it. Atrial fibrillation is almost invariably present. The

dullness in the right posterior chest may suggest effusion, and in two recorded cases (Owen and Fenton [1] and Bedford [2]), the left atrium was actually punctured during attempted paracentesis. The differential diagnosis includes enlarged right atrium, encapsulated pericardial fluid or pericardial cyst, aneurysm of the ascending aorta, and mediastinal tumors and cysts.[8]

Radiologically, in the frontal view the projecting left atrium in early stages reveals itself as a convex curve or double curve at the upper margins of the right atrium, thus forming part of the right border of the heart. In extreme cases the esophagus, when filled with barium, appears narrowed, constricted, and displaced posteriorly and to the right, and the postcardiac space is obliterated. The angle of bifurcation of the bronchi is directly related to the left atrial enlargement, and tendency toward an obtuse angle strongly suggests left atrial enlargement. Steele [9, 10] has shown the average of the angle of deviation of the main bronchi in mitral stenosis to be increased 30°.

Conclusions

1. Massive dilatation of the left atrium is considered a rare condition.
2. Massive dilatation of the left atrium represents an exaggeration of the enlargement seen in mitral stenosis.
3. Early diagnosis of massive enlargement of the left atrium depends almost wholly on roentgenologic studies.

Summario in Interlingua

Es presentate un caso de stenosis mitral, con le objectivo de illustrar le allargamento progressive del atrio sinistre que resultava in un dilatation massive. Isto es considerate como un occurrentia rar. Minus que 40 casos se trova reportate in le litteratura.

Un masculo de racia blanc, primo vidite al etate de 24 annos, esseva tenite sub observation con roentgenographia e examines physic durante un periodo de 12 annos. Ille esseva tractate pro rheumatic morbo cardiac (inactive), stenosis mitral, stenosis aortic, fibrillation atrial, disfallimento congestive, e progressive allargamento cardiac. Le final roentgenogrammas thoracic revelava un allargamento considerabile del corde in comparation con le stato de 12 annos retro. Un grande umbra in le thorace, que se misceva con le representation del corde e obscurava lo in parte, esseva visualisate per fluoroscopia e pareva representar un grande massa cystic. Isto esseva situate al dextera e in retro del corde, displaciante le corde in direction anterior e sinistrorse. Le esophago esseva displaciate verso le dextera e in direction posterior. Quando le patiente se trovava in postura erecte, un considerabile effusion al latere dextere oblitterava le angulo costophrenic e se extendeva usque al septime costa.

Le necropsia revelava un grande structura cystic in retro del corde. Illo circumdava le corde al latere dextere e displaciava le pulmon dextere in direction cephalic, de maniera que le lobo dextero-central esseva completemente atelectatic. Le lobo inferior esseva displaciate in direction cephalic foras del area del sulco dexterocostophrenic. Tamen, le structura cystic esseva recognoscite per dissection como le atrio sinistre que mesurava post fixation 20 per 15 per 10 cm. Illo contineva (estimatemente) inter 1.500 e 2.000 cm^2 de sanguine. Le valvulas mitral e aortic revelava ancian lesiones rheumatic e fibrotic. Sectiones del dilatate atrio sinistre monstrava spissification focal de endocardio, con reimplaciamento del pariete per histos fibrose in certe areas.

Iste dilatation massive representa un exaggeration del allargamento sinistro-atrial que es incontrate in stenosis mitral. Le diagnose precoce de iste condition depende quasi totalmente de studios roentgenologic.

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ACTH AND CORTISONE IN GUILLAIN-BARRÉ SYNDROME: REVIEW OF THE LITERATURE AND REPORT OF A TREATED CASE FOLLOWING PRIMARY ATYPICAL PNEUMONIA *

By Franz J. Berlacher, Captain (MC) USAR, and Robert B. Abington, Captain (MC) USA, *Honolulu, Hawaii*

Guillain-Barré syndrome is an uncommon, acute polyradiculoneuropathy characterized by a progressive motor and sensory disturbance of cranial and spinal nerves, with albuminocytologic dissociation of the spinal fluid.

Since Guillain, Barré and Strohl [1] described this syndrome in 1916, numerous articles have appeared in the literature under various titles, including: polyradiculoneuritis, myeloradiculitis, polyneuritis with facial diplegia, infectious polyneuritis, infectious neuronitis, and Landry's ascending paralysis. It is doubtful if this problem of nosology can be settled until more is known regarding etiology and pathogenesis, since the diagnosis at present is based on the clinical picture, the spinal fluid findings, and the progress of the illness.

Etiology

Specific toxins, viruses and bacteria, as well as dietary deficiencies, heavy metal poisoning and circulatory disturbances, have all been implicated in the

* Received for publication September 5, 1956.
Requests for reprints should be addressed to Captain Robert B. Abington (MC), Tripler Army Hospital, Box 173, APO 438, San Francisco, California.

past as being of etiologic importance. None, however, has been substantiated by good clinical or experimental evidence.

If specific peripheral neuropathic entities capable of producing a syndrome resembling that of Guillain-Barré are excluded (e.g., diabetes mellitus, porphyria, polyarteritis nodosa), then most of the remaining cases can be classified into three groups, as suggested by Crozier and Ainley [2]: (1) postinfectious, both viral and bacterial; (2) following drug or foreign protein administration, and (3) idiopathic.

The onset of the illness follows acute infections in 50% of the cases. This, together with the cases following the administration of drugs or foreign proteins, suggests the common denominator of an allergic or hypersensitive state analogous to rheumatic fever and serum sickness. Recent experimental work has supported this theory. Waksman and Adams [3] have produced in rabbits an experimental allergic polyneuritis by the injection of homologous and heterologous nerve extracts with adjuvants such as tubercle bacilli and mineral oil.

Pathology

The earliest neuropathologic findings in patients dying of Guillain-Barré syndrome are consistent with the proposed allergic etiology. According to Schienker [4] and Haymaker and Kernohan,[5] the outstanding feature early in the disease is the pronounced edema of the nerve fibers of the spinal roots and proximal portions of the cranial and peripheral nerves. Schienker has also described similar edematous involvement of the spinal cord tracts.

The axonal edema, with consequent sudden increase in bulk of most of the spinal roots, leads to narrowing and obliteration of the perineural spaces and, if more severe, to strangulation of the radicular trunks. As a result of the latter there is degeneration of the myelin sheath, with loss of nerve fiber function leading to an areflexic flaccid paresis or paralysis and the characteristic sensory disturbances. The inflammatory features in the peripheral nerves and central nervous system that have been described in the literature can be explained as being secondary to the retrograde cellular and myelin sheath degeneration.

Obliteration of the perineural spaces blocks the absorption of spinal fluid along these channels and leads to stagnation and trapping of the fluid within the subarachnoid space. The end result is then similar to that of a spinal fluid block produced by a space-occupying lesion. The classic albuminocytologic dissociation, almost universally observed in this syndrome, can be explained on the basis of this obstruction permitting escape of water and electrolytes, but not the large protein molecules. In addition, there may be a factor of capillary damage, with increased permeability and leakage of protein into the spinal fluid. The minimal-to-absent inflammatory involvement of the meninges is believed to explain the normal cell count usually observed. It should be emphasized, however, that lymphocytic pleocytosis is not unknown during the early stage of the disease, as in the case to be presented.

Clinical Picture

Guillain-Barré syndrome generally develops a few days to several weeks after a mild infection, usually of the respiratory or gastrointestinal tract. The

earliest neurologic symptoms are generally referable to the sensory system and characteristically limited to the distal portions of the extremities. From within a few hours to as long as one week following the sensory disturbance, motor signs make their appearance. These consist typically of bilateral, symmetric, progressive weakness and, later, flaccid paralysis, with more severe involvement of the proximal portions of the limbs. This almost always overshadows the sensory changes, though the severity may vary from only slight weakness to complete quadriplegia. Wasting and muscle spasm are seldom as severe as in poliomyelitis. The superficial and deep tendon reflexes are either diminished or absent, and no pathologic reflexes can be elicited. Involvement of the rectal or vesical sphincters occurs frequently in the more severe cases.

The sensory disturbances are often manifested only in a subjective manner, by numbness or paresthesias. However, there may be actual impairment in vibratory and position sense, or diminished perception of pain and light touch. Often there is marked muscle and nerve trunk tenderness.

Cranial nerve involvement occurs in 35 to 50% of the cases. Classically, this is manifested as a unilateral or bilateral peripheral facial palsy. Dysphagia and dysarthria are also very common. More rarely one sees involvement of the third, fourth, fifth, sixth or twelfth cranial nerves. Papilledema and optic neuritis may be seen infrequently.

Though the disease may be associated with visceral changes at postmortem examination, constitutional or systemic manifestations such as fever and leukocytosis are usually absent or mild. Tachycardia in the absence of fever is not uncommon, and may in some cases be related to focal myocarditis. Focal necrosis of the liver and adrenal cortex, and lower nephron nephrosis have been described at necropsy.

Diagnosis

The diagnosis of idiopathic Guillain-Barré syndrome may be made only after excluding specific neuropathic entities such as dietary deficiency, alcoholism, poisoning with heavy metals (e.g., lead and mercury), diabetes mellitus, porphyria, polyarteritis nodosa, and postdiphtheritic polyneuritis. Primary tumors of the central nervous system can usually be differentiated by alterations in pressure relationships and neurologic findings indicative of a localized lesion. Descriptions of this syndrome have appeared in the literature due to metastatic carcinomatous involvement of the spinal cord and nerve roots. The metastases were found at necropsy to have caused compression of the nerve roots leading to a picture analogous to and indistinguishable from that of Guillain-Barré syndrome.

The disease most frequently confused with this syndrome is acute anterior poliomyelitis, particularly of the bulbospinal variety. Although there are many differences between the two diseases, on occasion the diagnosis can be made only after many weeks of careful observation, or by specific serologic tests for poliomyelitis.

Prognosis

The course of the illness is quite variable. The usual duration is from three to six months, with a range of from two weeks to three years or more. Convalescence is slow, but only 5 to 10% of the patients surviving the acute illness have significant permanent residuals. The syndrome is not so benign as Guillain and his group first believed. Various large series of cases report a mortality

rate of from 14 to 42%, averaging about 20%. Death occurs usually within the first few weeks of illness, and may be attributed in most instances to respiratory failure or cardiovascular collapse.

Management: Review of Literature

In the past, the treatment of Guillain-Barré syndrome was largely supportive and symptomatic. It was felt by some that BAL and/or large doses of B complex vitamins were of value. Maintenance of good nutrition, reassurance, physical therapy and prevention of contractures or elongation of paretic muscles were the mainstays of treatment and are still of the utmost importance. In the more severe cases with respiratory muscle involvement, mechanical aids and tracheotomy have been life-saving. More recently, positive pressure breathing, with the use of aerosols, and exsufflators have been of great assistance in tiding the patient over the acute illness. Antibiotics are beneficial in the treatment of the complicating infections, usually of the respiratory or urinary tracts.

In 1952 Seltzer et al.[6] and Stillman and Ganong[7] reported, almost simultaneously, the first successful use of ACTH and cortisone in the treatment of Guillain-Barré syndrome. Since that time we have been able to collect from the British and American literature a total of 24 cases so treated, containing sufficient information to make possible an attempted evaluation of this therapy. The patient herein reported constitutes the twenty-fifth case of the series.

To better evaluate hormonal therapy the authors classified the patients into three major groups, dependent upon the stage of illness at the time of institution of ACTH or cortisone. Group I consists of 16 patients (cases 1 through 16) in whom therapy was begun while the neurologic disease was still progressive. Group II consists of six patients (cases 17 through 22) in whom the neurologic disease was stationary and of maximal degree. Group III consists of three patients (cases 23 through 25) in whom the disease had shown improvement prior to the institution of ACTH or cortisone therapy. This will be referred to as the convalescent group. Table 1 presents the basic information regarding these 25 cases. Table 2 summarizes the results of therapy.

From the data presented in table 2, ACTH or cortisone seems indicated in patients who have progressive neurologic disease. It appears more than coincidental that 87.5% of the 16 progressive cases had arrest of the disease upon institution of adequate therapy. In addition, 68.7% of the patients showed definite improvement within the first 48 hours. Two additional patients (12.5%) showed ultimate improvement, but no data were given to indicate the exact time of response. Statements were made, however, that marked improvement had occurred by the third and sixth days of therapy, respectively. One case showed arrest of progression but no improvement until the fourth day of treatment. Only two patients (12.5%) had continued progression of the disease in spite of therapy, and one of the two received comparatively small doses of ACTH (10 mg. intravenously daily). The second failure had been on maintenance cortisone for rheumatoid arthritis at the time of onset of the disease and did not respond at any time, even to an increased dosage of cortisone. These data seem all the more impressive when it is realized that patients with paralysis usually tend to remain clinically stationary for some weeks before spontaneous improvement occurs.

TABLE 1

Author	Duration of Therapy	Duration of Dis. before Therapy	Progression of Disease	Result within 48 Hrs.	Result after 48 Hrs.	Interval from Initial Therapy to Almost Complete or Complete Recovery	Comments
			Group I Progressive Disease				
1. Stillman and Ganong[7]	ACTH (16 da.) Cortisone (25 da.)	12 da.	+ +	++ ++	+++ +++	7 wks.—residual subjective weakness + paresthesias of right foot	Relapse on 10th day of ACTH therapy, with immediate response to cortisone
2. Seltzer, Lichty and Conn[6]	ACTH (5 da.)	14 da.	+	++	+++	4 wks.—100% return	
3. Newey and Lubin[12]	ACTH (11 da.) ACTH (22 da.)	23 da.	+ +	++ ++	+++ +++	5½ wks.—100%	Relapse in 10th wk.—immediate remission with ACTH
4. Blood, Locke and Carabasi[13]	ACTH (6 da.) ACTH (8 wks.)	26 da.	+ +	++ ++	+++ +++	?—but over 17 wks.—still residuals	Relapse 2nd day after ACTH stopped. ACTH re-instituted after 1 mo.
5. Fiese, Cheu and Radding[14]	Cortisone (2 mos.)	8 wks.	+	++	+++	2½ mos.—100% except numbness of feet	Associated with infectious mononucleosis
6. Drenick and Avol (case 1)[15]	Cortisone (30 da.)	3 da.	+	++	+++	2 mos.—only slight weakness	
7. Drenick and Avol (case 2)[15]	Cortisone (27 da.)	7 da.	+	++	+++	5 wks.—discharged but still improving	Associated with herpes zoster
8. Tupper and Foster[11]	Cortisone (2 wks. plus)	2½ wks.	+	++	+++	?	Increased dose from 300 to 500 mg. q.d., with more marked improvement
9. Crozier and Ainley (case 10)[2]	ACTH (many wks.)	7 da.	+	?	+++	3½ mos.—residual paresthesias only	Responded before the 6th day of therapy
10. Senseman and Greenstein (case 2)[16]	ACTH (14 da.) Cortisone (17 da.)	7 da.	+	++	+++	3 wks.—100% except slight numbness	

TABLE 1—(*Continued*)

Author	Duration of Therapy	Duration of Dis. before Therapy	Progression of Disease	Result within 48 Hrs.	Result after 48 Hrs.	Interval from Initial Therapy to Almost Complete or Complete Recovery	Comments
11. Senseman and Greenstein (case 3)[16]	Cortisone (8 da.)	3 wks.	+	?	+++	16 da.—100%, essentially	Responded by 3rd day of therapy at latest
12. Foster and Pokorny (case 1)[17]	ACTH (11 da.) Cortisone (? da.)	2–3 wks.	+	++	+++	1 mo.—residual fatigue + subjective generalized weakness	Relapsed 3rd day with inadequate dosage, improved with increased dose
13. Vernon[18]	ACTH (10 da.) Cortisone (20 da.)	19 da.	+	++	+++	15 da.—only mild left VII nerve palsy; 30 da.—100%	
14. Berlacher and Abington	Cortisone (44 da.) ACTH (3 da.)	10 da.	+	±	+++	8 wks.—85% return	Improvement noted 4th day of therapy
15. Foster and Pokorny (case 2)[17]	ACTH (7 da.)	5 wks.	−	−	Slow	25th day discharged, barely able to walk	Considered as therapeutic failure since only slow response from 8th da. of therapy. Dosage rather small
16. Grant and Leopold[19]	Cortisone (? da.)	0 da.	−	−	−	?—began to improve after 2 wks.	Was on maintenance cortisone for rheumatoid arthritis—no response to increased dosage
Group II Maximal Stationary Disease							
17. Plough and Ayerle[20]	ACTH (12 da.)	12 da.	Max. dis. 3 da.	++	+++	3 mos.—100% muscle strength	Associated with hepatitis
18. Plum (case 1)[8]	Placebo (3 da.) Cortisone (9 da.) Placebo (14 da.) Cortisone (14 da.)	50 da.	Max. dis. 5 wks.	± ++ − − ++	± +++ − − +++	2½ mos.—essentially 100%	Relapsed with 2nd placebo course; responded both times to cortisone
19. Plum (case 2)[8]	Placebo (4 da.) Cortisone (9 da.) Cortisone (18 da.)	6 mos.	Max. dis. 1 mo.	± ± ±	+++ +++	3 mos.—returned to duty	Responded on 4th and 5th days to cortisone, respectively, with relapse after 1st course of therapy

TABLE 1—(*Continued*)

Author	Duration of Therapy	Duration of Dis. before Therapy	Progression of Disease	Result within 48 Hrs.	Result after 48 Hrs.	Interval from Initial Therapy to Almost Complete or Complete Recovery	Comments
20. Plum (case 3)[8]	Cortisone (8 da.) Cortisone (8 da.) Cortisone (8 da.)	2 mos.	Max. dis. 3 wks.	±	±	?	Therapeutic failure; 5 day intervals between each of 3 courses of cortisone
21. Senseman and Greenstein (case 1)[16]	ACTH (47 da.) ACTH (20 da.)	2 mos.	Max. dis. 1 mo.	± ?	+++ +++	?—discharged 4th mo.	Responded 3rd day of therapy; relapsed when ACTH stopped but again responded to ACTH
22. Clarke, Bayliss and Cooper (case 2)[21]	Cortisone (? da.)	2 mos.	Less than 1 mo. Max. dis.	±	Slight	6 mo.—minimal residuals	Cardiovascular response to cortisone. No definite neurologic response
			Group III Convalescent Disease				
23. Clarke, Bayliss and Cooper (case 3)[21]	Cortisone (? da.)	3 mos.		±	±	4 mos.—slow improvement	Cardiovascular response noted. No definite response in neurologic disease
24. Crozier and Ainley (case 9)[2]	ACTH (? da.)	?		±	±	9 mos. from onset of disease, slight calf weakness	No evidence of cortisone-accelerated recovery
25. Feldman, Landau and Halpern[22]	ACTH (5 da.)	Greater than 6 mos.		±	±	2½ years, still marked residuals	No response to ACTH or BAL therapy

Abbreviations:

da. = day.
wk. = week.
mo. = month.
? = insufficient data.
− = worse.
± = no change.
+ = arrested.
++ = improved.
+++ = continued improvement.

Four of these patients had relapse of their disease. Two relapsed while on inadequate therapy, as judged by the immediate improvement following increase in dosage of ACTH or changing from ACTH to cortisone. The other patients relapsed two days and 10 weeks, respectively, following cessation of ACTH. Both patients showed immediate and continued improvement following re-institution of ACTH therapy.

Cortisone or ACTH is probably worthy of at least a clinical trial in patients with stationary but maximal disease. Of the six patients in this group, only two (33.3%) showed improvement within the first 48 hours. Two additional cases improved on the third and fourth day of therapy, respectively. No definite response was noted in neurologic disease in the two remaining cases. Plum's [8] placebo studies in cases 18 and 19 showed a definite therapeutic response to

TABLE 2

Results of Therapy

	No. of Cases	Per Cent
Group I—Progressive Disease (Cases 1 through 16)	16	
1. Arrest of progression	14	87.5
2. Response within 48 hours		
(a) Improved	11	68.7
(b) No data	2	12.5
(c) No improvement	1	6.3
(d) Worse	2	12.5
3. Response after 48 hours		
(a) Improvement	14	87.5
(b) No response	2	12.5
Group II—Maximal Stationary Disease (Cases 17 through 22)	6	
1. Response within 48 hours		
(a) Improved	2	33.3
(b) No response	4	66.7
2. Response after 48 hours		
(a) Improvement	4	66.7
(b) No response	2	33.3
Group III—Convalescent (Cases 23 through 25)	3	
1. No response at any time	3	100%

cortisone, and represented the only attempt at a controlled study in this syndrome.

Therapy in the so-called convalescent group seems to be of no value, though admittedly this conclusion is based on a series of only three cases.

Several other points seem worthy of comment. Most of the reported patients were severely ill. Several required respiratory aids and two, in addition, showed cardiovascular collapse. The reported mortality averages about 20%, yet in these 25 patients there were no deaths. The patients in Group I had, in general, a somewhat shorter duration of illness following institution of ACTH or cortisone therapy than did patients in Group II or III. The total duration of illness appeared to be somewhat shorter than the usual three to six months stated by Brain.[9] In several cases a prompt drop in spinal fluid protein was noted concomitant with a hormone-induced remission. This is a distinctly unusual occurrence in untreated patients.

Five patients with Guillain-Barré syndrome treated by Eaton, and cited as a

personal communication in Plum's article, and two patients reported by Merritt [10] showed no response to ACTH or cortisone therapy. For these seven patients, however, no information is available concerning dosage or stage of illness at time of initial therapy. If treatment was begun in the convalescent stage of the disease no improvement should be anticipated, and they would therefore not represent a true therapeutic failure.

It is difficult to make specific recommendations from available data as to exact dosage of cortisone or ACTH, or optimal duration of administration. In general, it is probably best to begin with about 300 mg. of cortisone for the first few days. If no response becomes evident within two to four days a trial of 500 mg. cortisone per day may be indicated, since in Tupper and Foster's [11] patient an increase in response was noted with this larger dose. Cortisone should then be reduced to a maintenance level of 100 to 200 mg. per day and continued for from two to four weeks. Following this it may be reduced by decrements of 12.5 to 25 mg. every third day. The entire course should last four to eight weeks, depending upon clinical response. If relapse occurs either following cessation of therapy or because of inadequate dosage, re-institution or increase in dose is indicated. From the available information it appears that if there is no response within the first week of adequate therapy, then nothing is to be gained by continuing drug administration.

ACTH, in comparable dosage, is probably as satisfactory as cortisone, though in Stillman and Ganong's patient cortisone brought about continued improvement after relapse on ACTH. This was apparently due to inadequate adrenal response to ACTH, as judged by serial total eosinophil counts.

If the etiology of this syndrome is an allergic phenomenon, as has been proposed, then the results in the three major groups seem understandable. In the progressive cases one would expect the major pathologic process to be an axonal edema which would be reversible with hormonal therapy. The maximal stationary group would probably be characterized by a combination of edema plus secondary nerve degeneration resulting from the chronic nerve root strangulation. ACTH and cortisone would then be of value only in reversing that portion of the neurologic manifestations produced by edema. The convalescent group would be characterized by residual secondary nerve degeneration and completely unresponsive to hormonal therapy.

Case Report

History and Physical Examination: A 25 year old naval officer was hospitalized on February 21, 1956, with a nine day history of low grade fever, tightness in the chest and dry cough, associated with progressive generalized malaise, headache, arthralgia and myalgia.

Positive physical findings on admission included a markedly irritable, lethargic male with a temperature of 100.4° F. There was slight injection of the posterior pharynx. A few scattered crepitant and subcrepitant râles were heard over the right midlung posteriorly. The liver was palpable 2 cm. below the right costal margin and was minimally tender. The remainder of the physical examination, including the neurologic, was within normal limits.

Laboratory Data: Studies on the day of admission revealed the following: The hematocrit was 46%; total white count, 12,500; 79% neutrophils, 18% lymphocytes,

2% monocytes, and 1% eosinophils; normal urinalysis; negative cardiolipin. Sputum and throat cultures revealed no pathogenic organisms. Chest roentgenogram on the day of admission demonstrated an infiltration in the right midlung field. A progress chest roentgenogram on February 27 was normal. Serial cold hemagglutination titers were: February 21, 1:10; February 29, 1:40; March 2, 1:80; March 6, 1:64; March 29, 1:32; subsequent titers were negative. Streptococcus M. G. titers were: February 24, 1:32; March 6, 1:32; March 28, 1:8. Spinal fluid studies on February 23 revealed the following: white cell count, 128; 91% lymphocytes; protein, 102 mg.%; sugar, 66.8 mg.%; chlorides, 117 mEq./L.; negative smear and culture. Repeat examination on February 29 showed an opening pressure of 220 mm. water; total white count, 15; 1 neutrophil, 14 lymphocytes; total protein, 348 mg.%; sugar and chlorides, normal. Follow-up spinal fluid examinations on March 23 and April 9 were normal except for proteins of 208 and 106 mg.%. Other laboratory data consisting of serial complete blood counts, heterophil agglutination, serum bilirubin and cephalin cholesterol flocculation were within normal limits. Serologic studies on acute and convalescent sera were negative for Q-fever, psittacosis-lymphogranuloma venereum group viruses, leptospira, and lymphocytic choriomeningitis.

Course in Hospital: After initial bacteriologic studies were obtained the pneumonitis was treated with streptomycin and penicillin. The patient remained afebrile after the fifth hospital day, and subsequent examinations of the chest were normal.

On February 23, 36 hours following hospitalization, the patient began to complain of coldness of the extremities limited to the stocking-glove areas, and difficulty with urination which necessitated catheterization. He continued to manifest marked irritability and lethargy. No nuchal rigidity was noted; however, the patient demonstrated tripoding, with spasm of the lumbar paraspinal and hamstring muscles. There was no gross evidence of muscle weakness or fasciculation. Cranial nerves were intact. Only six hours later, neurologic examination revealed the following abnormalities: absent left abdominal and cremasteric reflexes, hypoactive reflexes of the right leg, and spotty areas of anesthesia over the left leg. Marked progression occurred during the next nine days, with complete left facial paralysis and severe symmetric paresis of all four extremities, back, shoulder girdles, and abdominal musculature. Primary muscles of respiration were clinically uninvolved. All deep tendon and superficial reflexes were absent. No pathologic reflexes were elicited. Examination of various sensory modalities showed only spotty areas of anesthesia over both lower extremities.

Because of the continued progression of the disease, cortisone therapy was begun on March 3. This consisted of 300 mg. cortisone daily for one week, followed by 200 mg. per day for one month. Dosage was then gradually reduced by decrements of 25 mg. Twenty-four hours after initiation of therapy, lethargy and irritability had cleared remarkably. Generalized weakness improved only subjectively. Detailed muscle evaluation by the Department of Physical Medicine at this time still revealed generalized muscle weakness averaging 40 to 50% of normal in the involved muscles of the trunk and extremities. Left facial paralysis improved rapidly after four days of cortisone, with essentially complete return after two weeks. Other muscles showed a more gradual improvement, and on March 27 a repeat detailed evaluation revealed a return of muscle strength to 70% of normal. By April 15 the patient was completely ambulatory. Muscle evaluation on April 28 showed an average return to 85% of normal. Further convalescent care was continued on an out-patient status. By the end of May, muscle function had returned to essentially 100% of normal.

Total course of hormonal therapy was 44 days. Supplementary ACTH was administered during the last few days of cortisone therapy. Acneform eruptions over the face and back and a suggestion of moon facies were the only significant side reactions noted.

Comments

The central nervous system complications of primary atypical pneumonia have been recently reviewed by Yesnick. Of 38 cases reviewed, 24 manifested a meningo-encephalitis, five transverse myelitis, four hemiplegia, four ascending paralysis, and one cranial nerve palsy. Of the four cases of ascending paralysis, two reported by Owen [31] and Chang [32] fitted the criteria for the diagnosis of Guillain-Barré syndrome. This case is then the third such complication following proved primary atypical pneumonia.

Summary

1. Guillain-Barré syndrome has been reviewed with emphasis on the etiology and pathogenesis.

2. Twenty-four patients with Guillain-Barré syndrome treated with ACTH and cortisone reported in the literature and one treated by the authors have been reviewed. Therapy seems indicated in the progressive phase of the illness, worthy of at least a clinical trial in the maximal stationary stage of the disease, and of no apparent benefit in convalescent patients.

3. A program of drug management is proposed.

4. A case with proved primary atypical pneumonia complicated by Guillain-Barré syndrome and treated with cortisone is presented in detail.

Summario in Interlingua

Le etiologias de syndrome de Guillain-Barré pote esser classificate como (1) post infectiones (tanto virusal como etiam bacterial), (2) post administration de drogas o corpores alien, e (3) idiopathic.

Le pathologia e le pathogenese del morbo pote esser explicate per le disveloppamento de edema axonal con strangulation del trunco nervose. Isto es sequite per un degeneration secundari del nervos. Le oblitteration del spatios perineural resulta in un bloco functional con le characteristic valores elevate pro proteina in le fluido spinal.

Le duration del morbo pote esser ab tres a sex menses. Un residuo de injurias neuromuscular es presente in inter 5 e 10 pro cento del casos. Le mortalitate amonta a un valor medie de 20 pro cento.

Le tractamento de iste syndrome con ACTH o cortisona es discutite super le base de un studio de 25 casos in le litteratura de lingua anglese, incluse le caso hic reportate.

Dece-sex patientes esseva tractate durante le phase progressive de lor morbo neurologic. Responsas intra 48 horas esseva notate in 11 casos. In tres casos, nulle melioration o mesmo un continue progresso del morbo esseva notate. Dece-quatro patientes monstrava definite grados de melioration intra plus que 48 horas.

In sex del patientes tractate, le morbo esseva considerate como stationari e de grado maximal. Duo ex iste gruppo monstrava melioration intra 48 horas.

Therapia a hormones esseva usate in tres patientes post que le symptomas neurologic habeva comenciate meliorar se. Nulle definite responsa a iste tractamento esseva reportate.

Ab iste datos il es apparente que ACTH e cortisona es benefic in patientes con progressive morbo neurologic. De accordo con le conceptos del pathogenese, le edema axonal deberea esser reversibile con therapia hormonal. Le combination de edema e degeneration nerval es forsan solmente reversibile in parte in patientes con morbo stationari maximal. Tamen, ACTH o cortisona merita probabilemente un

essayo clinic. In patientes convalescente con residue degeneration nerval secundari, therapia a hormones pare esser sin valor.

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ACUTE GOUT ASSOCIATED WITH CHRONIC MYELOGENOUS LEUKEMIA *

By Frank M. Blanton, M.D., *Richmond, Virginia*

Myelogenous leukemia and gout, two distinct diseases of unknown etiology, have in common a disorder of uric acid metabolism which is manifested clinically by an elevation of the blood uric acid. The simultaneous occurrence of these two otherwise unrelated diseases is of interest and is illustrated by the following case report.

Case Report

A 72 year old Negro male was admitted to the Medical College of Virginia Hospital in March, 1952. He gave a two-week history of chest pain, cough, fever, chills, dyspnea and hemoptysis. On examination the temperature was 100.8° F.; pulse, 88; respiration, 20; blood pressure, 160/80 mm. of Hg. The eyes, ears, nose and throat were not remarkable. The heart was normal. Scattered rhonchi were heard throughout the chest. The liver and spleen were both palpable. Laboratory studies revealed a normal urine, a hemoglobin of 11.8 gm. and a white count of 52,000. The blood smear revealed a predominance of mature polymorphonuclear cells, although some younger myeloid cells were seen. An occasional myeloblast was present. A bone marrow preparation revealed myeloid hyperplasia and erythroid hypoplasia.

A diagnosis of chronic myelogenous leukemia complicated by acute bronchopneumonia was made. The pneumonia responded rapidly to antibiotics, and the patient was then treated with x-ray therapy over the spleen. He was discharged from the hospital and followed in the blood and spleen clinic. He did well, but required small doses of x-ray over the spleen approximately every four to six months. White blood counts ranged from 18,000 to 195,000.

* Received for publication October 12, 1956.
From the Blood and Spleen Clinic, Outpatient Department, Medical College of Virginia Hospital.
Requests for reprints should be addressed to Frank M. Blanton, M.D., 828 West Franklin Street, Richmond 20, Virginia.

In February, 1956, the patient complained of malaise and his white count was found to have risen to 90,000. He was given x-ray therapy over the spleen and returned home. The following day he developed severe, excruciating pain in the first metatarsophalangeal joints of both feet. These joints were said to be red, hot and extremely tender to the touch. He was seen by his physician in the country and given pills to take. These were apparently colchicine. He was instructed to take one every hour until the pain was relieved or he became nauseated. After four or five doses the inflammation cleared on the right, but because of nausea he stopped the medicine. He was seen one week later in the Blood and Spleen Clinic of the Medical College of Virginia, where a bluish red swelling was noticed over the left first metatarsophalangeal joint. This was still moderately tender. Blood for uric acid was drawn and found to 8.3 mg./100 c.c. The white count had fallen to 47,000. He was given another course of colchicine, and one week later the podagra had completely subsided. The uric acid had fallen to 4.3 mg./100 c.c.

Discussion

It is a well known fact that in leukemia the serum uric acid is elevated and at times is quite high. It is also well known that gout is a disease characterized by an elevated uric acid in the blood and attacks of acute arthritis due to deposition of uric acid crystals in and about joints. It would seem logical to find gout often complicating leukemia. Frequent statements in the literature seem to bear this out. Thorn,[1] in Harrison's *Textbook of Medicine,* states that certain diseases appear to be associated with gout more often than one would expect simply by statistical chance. These include diabetes mellitus, leukemia, polycythemia vera, pernicious anemia and Paget's disease. Barrick and Miller,[2] in a review of gout, state that the three most common types of blood diseases in which there are hyperuricemia and gout are leukemia, familial hemolytic jaundice and pernicious anemia.

More careful review of the literature, however, indicates that this is a not so common occurrence. Forkner [3] states that the simultaneous occurrence of gout and leukemia is so rare that any real relationship seems doubtful. Wintrobe [4] says that gout in leukemia is rare. Shorvon [5] in 1946 reported an attack of gout in a 37 year old male following x-ray therapy for chronic myelogenous leukemia. He reviewed the literature prior to this time and could find only five cases of gout and leukemia. In 1950 McEwan [6] reported a case with gouty tophi and chronic gout which followed shortly after x-ray therapy. A review of the literature to date reveals no other cases of leukemia and gout.

Gout at times is associated with other hematologic conditions having a high serum uric acid. Tinney, Polley, Hall and Giffin [7] found eight cases of gout out of a series of 168 cases of polycythemia vera. Hickling [8] states that myeloid metaplasia is not uncommonly complicated by gout, and reports several cases illustrating this. Recently Bronsky and Bernstein [9] reported a case of acute gouty arthritis in a 68 year old Jewish male with multiple myeloma.

The elevated serum uric acid in leukemia is thought to be related to the increased catabolism of nucleoprotein of the leukemic cells. X-ray and chemical therapy of leukemia causes a marked rise in uric acid excretion [10, 11] which parallels the destruction of white cells. Theoretically, gout should be a frequent complication of leukemia and its therapy. The previously cited few cases, however, indicate that this occurs rarely in spite of the frequent elevation of uric acid in the blood.

There is no agreement in the literature as to whether the hyperuricemia of blood dyscrasias causes the gout or is a chance occurrence. Forkner [3] is of the opinion that the relationship is coincidental. Shorvon [5] felt that on rare occasions gout could result purely from the hyperuricemia of leukemia. Tinney et al.[7] felt that the only effect was to aggravate or precipitate an attack in a person with the gouty diathesis.

The frequent finding of elevated uric acid in blood dyscrasias and the relative rarity of gout seem to indicate that there is more to gout than simply the level of uric acid in the serum. It seems necessary to postulate a diathesis to uric acid deposition and arthritis in addition to the metabolic defect. It is most probable that the cases discussed here represent people with the gouty diathesis who have developed leukemia. The subsequent increased nucleoprotein catabolism has precipitated an attack of gouty arthritis.

Summary

A case of gout occurring after x-ray therapy for leukemia has been reported. The relationship between these two diseases has been discussed, and the relative infrequency of their simultaneous occurrence has been pointed out.

Summario in Interlingua

Leucemia myelogene e gutta—distincte morbos de etiologia non cognoscite—ha in commun un disordine del metabolismo de acido uric. Es presentate un caso in que un masculo negre de etate avantiate qui suffreva de leucemia myelogene disveloppava acute arthritis guttose post un curso roentgenotherapeutic antileucemic. Viste que ambe iste morbos se manifesta clinicamente in elevate nivellos de acido uric in le sanguine, il pare logic expectar un occurrentia frequente de gutta como complication de leucemia. Multe assertiones in le litteratura tende a reinfortiar iste conception. Tamen, un revista del reportos mesme indica que le association es plus tosto rar. Non plus que septe casos de gutta associate con leucemia es mentionate in previe publicatones, e le caso hic reportate es le tertie in que un attacco de gutta sequeva le roentgenotherapia de leucemia. Gutta es a vices associate con altere conditiones hematologic que se distingue per un alte nivello de acido uric in le sero. Iste association ha essite reportate pro polycythemia ver e pro casos de metaplasia myeloide. Recentemente un attacco de gutta esseva reportate como complication de myeloma multiple. Le elevate nivello seral de acido uric in leucemia es relationate a un augmentate catabolismo de nucleoproteina, e roentgenotherapia augmenta iste catabolismo considerabilemente. Le raritate relative de arthritis guttose post tractamentos pro chronic leucemia myeloide pare indicar que le etiologia de gutta es plus complexe que simplemente un disturbate metabolismo de purina con excessive reservas de acido uric. Il etiam debe esser postulate que il existe un diathese pro gutta con deposition de acido uric in le articulationes. Il es probabilissime que le patientes in le casos hic discutite esseva individuos con diathese guttose qui disveloppava leucemia.

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MYOCARDIAL ISCHEMIA: REPORT OF A CASE DUE TO REACTION TO TETANUS ANTITOXIN *

By Ray L. Casterline, M.D., F.A.C.P., *Medford, Oregon*

The current medical literature has been adequately documented with specific instances of profound allergic reaction to penicillin and other antimicrobial agents.[1, 2] This case is presented to emphasize that allergic reactions to tetanus antitoxin do occur in spite of apparently adequate testing with horse serum prior to administration of the antitoxin. These reactions, when they occur, often fit the picture of serum sickness and may involve wide areas. They are often basically vascular in nature [3] and capable of producing considerable injury in the areas affected by the vascular phenomena, although most of the lesions appear to be reversible. This case is of interest in that serial electrocardiographic study indicated the deep-seated ischemic nature of the process and showed a pattern resembling that seen in recent posterior myocardial infarction.

Case Report

The patient, a 43 year old white laborer, had had a portion of his left middle finger amputated at the Ashland (Oregon) General Hospital on January 31, 1956. At the time of the amputation he was given tetanus antitoxin after apparently adequate skin testing procedures; no penicillin was administered. Following a period during which he had been free of any symptoms, he developed generalized urticaria, joint distress and wheezing on February 8, 1956. He was admitted to the Rogue Valley Memorial Hospital, Medford, Oregon, on February 9, 1956, and was seen in medical consultation later that morning.

His past personal history revealed only a hemorrhoidectomy in 1947. Otherwise he had experienced no serious illnesses or operations. There was no history of abnormal vascular phenomena in his family, nor was there any remarkable allergic background.

When seen, the patient presented the picture of shock, with a blood pressure

* Received for publication September 10, 1956.
Requests for reprints should be addressed to Ray L. Casterline, M.D., 832 East Main Street, Medford, Oregon.

of 60/40 mm. of Hg, thready pulse with a rate of 120 per minute, and an oral temperature of 98.2° F. His skin was moist, blotchy and reddened between areas of giant hives.

There was moderate puffiness over the upper eyelids, but no other striking abnormalities were noted. There was no arcus senilis. The ocular fundus showed no vascular abnormalities. The tongue and the mucous membranes of the mouth and pharynx were edematous. There were moist râles at the right lung base, and coarse rhonchi were heard throughout both lung fields. The heart was of the transverse type and of normal size. The tones were not distinct. There was no notable enlargement of the liver or spleen, and no unusual masses were felt in the abdomen. Examination of the extremities revealed amputation of the midfinger, left hand, at the distal interphalangeal joint, with healing progressing adequately.

Routine laboratory studies showed a red blood count of 5,400,000; hemoglobin, 16.4 gm.; white blood count, 6,200, with a normal differential distribution. The sedimentation rate was 30 mm. at 60 minutes. The urine showed a specific gravity of 1.025, no reduction, no albumin; microscopic examination showed no abnormality. The serologic test for syphilis was negative.

An electrocardiogram taken shortly after admission showed a sinus tachycardia and low voltage to iso-electric T waves in Lead I. There was apparent elevation of the S-T segments in Leads II and III, and the T waves were sharply inverted and coved. A tiny Q wave was apparently present in Lead II and in aV_F, where there were prominent R waves, a moderate S-T segment elevation and a coved, negative T. The T waves were inverted, appeared coved in V_4, and of low voltage throughout the remaining precordial leads. The pattern was interpreted as indicative of injury to the posterolateral wall of the left ventricle, certainly more than highly suggestive of widespread myocardial injury.

Because of the apparent allergic reaction present, treatment was predicated upon the control of this problem. Following 75 units of ACTH given intravenously the blood pressure rose slowly, and then more rapidly following 30 mg. of l-arterenol given intravenously. The urticaria, joint symptoms and shortness of breath, together with the other physical findings noted above, became much less evident immediately following the ACTH.

An electrocardiogram taken the following day showed somewhat less inversion of the T waves in Leads II, III and aV_F and across the precordium. In V_4 the T wave was definitely upright, and on the fourth day the electrocardiogram was approaching a normal pattern, with normal S-T segments and upright T waves in the leads noted to be abnormal previously.

Following the initial doses, no further adrenocorticotropic hormone or adrenal cortical steroids were used, and antihistaminics readily controlled the reaction. The blood pressure stabilized near 120/80 mm. of Hg, and no additional generalized allergic reaction appeared.

In addition to the patient's apparent myocardial injury, the day after the onset of the generalized reaction a definite visual field defect was noted. It was the opinion of the consulting ophthalmologist that a right homonymous hemianopsia was present, due to ischemic change in the area supplied by the posterior cerebral artery. It was the ophthalmologist's further confirmatory opinion that no significant retinal arteriosclerosis was present.

Electrocardiograms were taken at frequent intervals and, following return of the electrocardiographic pattern to normal, the patient was discharged from the hospital on February 15, 1956, free of any symptoms, and without specific medication.

Subsequent follow-up in the office, with frequent examinations and serial electrocardiograms, has produced no further evidence of vascular disease, and the electrocardiograms have remained normal. Approximately six weeks following the onset

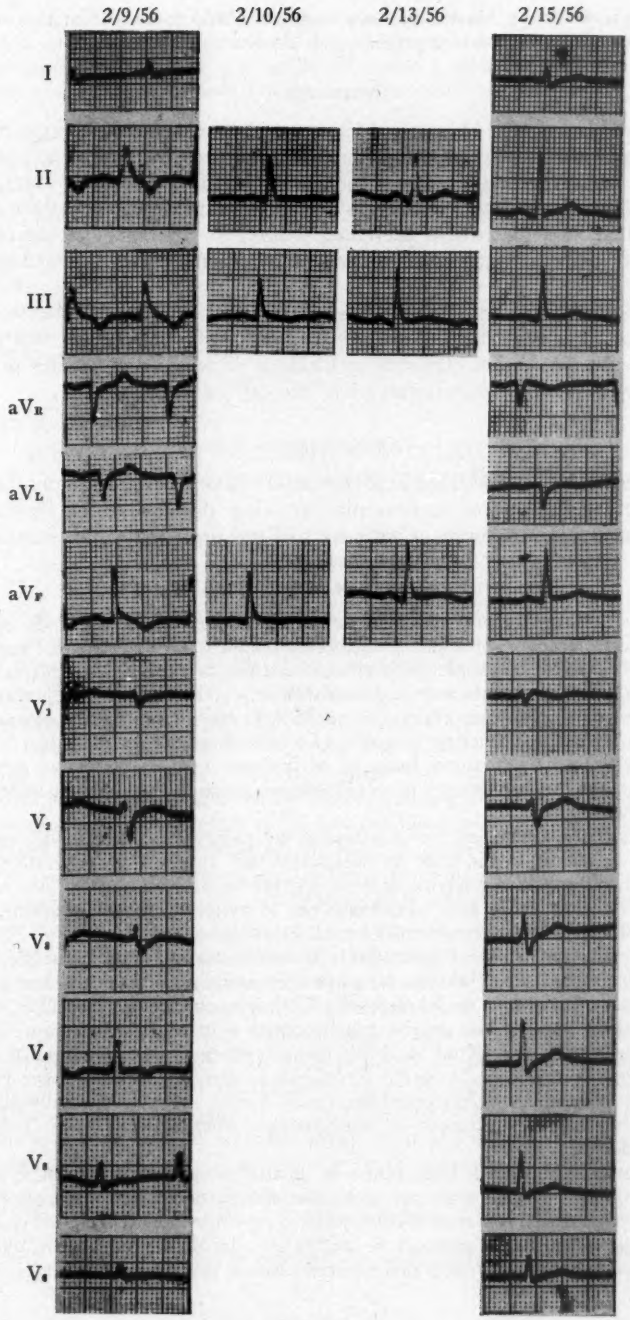

FIG. 1.

of the allergic process a Master two-step test was found to be within the range of normal. The visual field defect persists and has shown no change.

Summary

The case history of a 43 year old laborer with a widespread allergic reaction has been presented. The importance of immediate treatment with adrenocorticotropic hormone and vasopressor substance is emphasized.[4] Such therapy correlated well with the improvement in the electrocardiographic pattern. It is presumed that, had the patient presented himself for treatment at the onset of the reaction, many of the ischemic changes would not have occurred or been so severe.

The purpose of presenting this case is to point out that reactions of this type do occur, that they are widespread in their manifestations, and that prompt treatment with medication currently available is capable of producing profound changes and reversal of manifestations of the disease process.

Conclusion

The case history is presented of a 43 year old laborer with a profound allergic reaction to tetanus antitoxin, ischemia involving principally the myocardium and cerebrum, and improvement with ACTH and pressor substances.

Summario in Interlingua

Es presentate le historia del caso de un travaliator de 43 annos de etate qui disveloppava un reaction profunde a antitoxina tetanic. Le objectivo del reporto es monstrar que tal reactiones allergic continua occurrer in despecto de apparentemente adequate tests con sero equin ante le administration del antitoxino. Le presente caso esseva typic pro le genere de allergia in question in tanto que manifestationes esseva evidente de un extense reaction vascular. Le caso meritava un interesse special in tanto que electrocardiogrammas indicava le fundamentalmente ischemic natura del processo per exhibir initialmente un configuration simile a illo vidite in infarcimento postero-myocardial.

A parte le apparente lesiones myocardial del patiente, un defecto del campo de vision esseva notate le die post le declaration del reaction generalisate. Esseva trovate un hemianopsia homonyme dextere, e il esseva conjecturate que isto esseva le effecto de ischemia in le area alimentate per le arteria cerebral posterior. Nulle grados significative de arteriosclerosis retinal esseva presente.

Le tractamento includeva initialmente le administration intravenose de hormon adrenocorticotropic. Le pression sanguinee cresceva plus rapidemente post administrationes intravenose de *l*-Arterenol. Urticaria, symptomas articular, dyspnea, e le anormalitates physic que occurre usualmente in le presentia de extense reactiones allergic, deveniva multo minus evidente immediatemente post le administration de ACTH. Post le prime die, le problema esseva facilemente maneabile per medio de therapia antihistaminic. Electrocardiogrammas diurne revelava un melioration progressive. Intra duo septimanas le configuration electrocardiographic habeva retornate al norma.

Debe esser sublineate le importantia de un tractamento immediate in le presentia de tal reactiones. Il pote esser presumite que si le patiente se habeva presentate al consulta al tempore del declaration del symptomas e si ille habeva recipite ACTH e un agente vasopressori immediatemente in loco de attender un die, multes del alterationes ischemic non haberea occurrite o non haberea essite si sever.

Le presentation del caso hic reportate illustra le facto que reactiones de iste typo —si e quando illos occurre—es extense in lor manifestationes e que le prompte application del medicamentos nunc disponibile es capace a effectuar profunde alterationes e le reversion de multes del manifestationes del processo.

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HYPERPARATHYROIDISM WITHOUT BONE OR KIDNEY MANIFESTATIONS *

By Lester Rich, M.D., Jack Gordon, M.D., and Toby Freedman, M.D.,
Los Angeles, California

The parathyroid glands were first described in 1880 by Ivar Sandstrom after a series of cadaver dissections. Ten years later von Recklinghausen reported three probable examples of hyperparathyroidism, emphasizing the bony changes. Erdheim in 1906 was the first to relate calcium metabolism to the parathyroid glands. In 1924 and 1925 Hanson [1] and Collip [2] isolated the parathyroid hormone and demonstrated the elevation of serum calcium following injection of this hormone. The first successful surgical removal of a parathyroid tumor was accomplished by Felix Mandl in 1924.

The stimulus of Albright's work has produced a large literature describing the physiologic mode of action of parathyroid hormone, the clinical syndrome of hyperparathyroidism, the associated chemical aberrations, and the surgical treatment and postoperative care. Albright [3, 4] and others [5, 6, 7, 8] have pointed out that the clinical picture represents a composite of symptoms and signs of hypercalcemia per se, bone disease and kidney disease to the extent that these may be found in any individual with hyperfunctioning parathyroid glands.

By 1955 about 750 cases of hyperparathyroidism had been reported, 97 to 98% of whom have had either bone or kidney complications, or both. This report describes two patients with hyperparathyroidism without apparent manifestations of either bone or renal complications of the disease. These cases are of interest because of the paucity of such descriptions in the literature, and because they present certain features which may aid in the recognition of such cases before irreparable renal damage or death ensues.

* Received for publication October 5, 1956.
From the Departments of Internal Medicine and Pathology, Southern California Permanente Medical Group, Los Angeles, California.
Requests for reprints should be addressed to Lester Rich, M.D., 16161 Ventura Boulevard, Encino, California.

Case Reports

Case 1. A 58 year old white female was admitted to the Kaiser Foundation Hospital on June 2, 1955, with complaints of lower abdominal pain, anorexia, weakness and weight loss. She had felt well until two months prior to admission, when she developed a mild sore throat with some hoarseness, and nonbloody diarrhea of four to six watery brown stools daily. This was at first considered to be a viral gastroenteritis, and she was given symptomatic therapy. The diarrhea persisted for about one month and was associated with anorexia and a progressive weight loss of 17 pounds (122 to 105) during the two months prior to admission. Two weeks before admission she developed a fever up to 102.2° F. orally, associated with nausea, vomiting one to two times daily, and mild lower abdominal cramping pain. She was given two injections of penicillin and penicillin tablets orally for several days. The fever subsided, but the anorexia, nausea, vomiting, weakness and weight loss continued. The weakness became so profound that she had been bedfast for two weeks before admission. On the day of admission she developed moderately severe cramping left lower quadrant pain.

Past history included an appendectomy in 1941, with removal of a uterine myoma at the same time, a dilatation and curettage in 1944 for menorrhagia, a hemorrhoidectomy in 1933, and jaundice for about one week at the age of seven. She had been told many years before that she had a slightly enlarged heart, but had had no cardiorespiratory symptoms at any time. Her menopause had occurred in 1952.

Physical examination revealed a well developed, pallid, weak white female with signs of weight loss and moderate dehydration who appeared chronically ill. Temperature was 97.2° F. orally. There was no significant adenopathy. Head, eyes, ears, nose and throat were essentially negative. The right lobe of the thyroid was slightly irregular, but there were no definitely palpable nodules. Neck was supple. Lungs were clear to percussion and auscultation. The point of maximal impulse was in the midclavicular line, there was regular sinus rhythm (rate, 96), a soft apical systolic murmur, and the heart tones were of good quality. Blood pressure was 120/50 mm. of Hg. The liver was palpable one fingerbreadth below the right costal margin; it had a firm, sharp edge and was not tender. The spleen was not palpable. There was marked involuntary muscle guarding in the left lower quadrant, with direct and rebound tenderness and active peristalsis. Rectal examination showed a rosette of external hemorrhoids; no masses were palpated, but there was a feeling of fullness and moderate tenderness in the left side of the rectovaginal pouch. The cervix and vaginal mucosa were atrophic; the corpus was of normal size, anterior and mobile. The right adnexa was clear; the left felt indurated, tender and full. Deep tendon reflexes were normal.

Laboratory data on admission: hemoglobin, 11.1 gm.; white blood count, 11,300, with a normal differential. Urine was clear, with a specific gravity of 1.007, an occasional white blood cell per high power field, and no sugar or albumin. Serology was negative. Agglutinations for typhoid, paratyphoid, pasteurella, heterophil, Weil-Felix and Brucella, were negative. Four blood cultures showed no growth. Stools were negative for ova and parasites. Protein-bound iodine was 6.8 μg/100 ml.; blood urea nitrogen, 17 mg./100 ml.; sodium, 146 mEq./L.; potassium, 4.3 mEq./L.; chloride, 99 mEq./L.; CO_2, 27 mEq./L. Chest x-ray on admission showed clear lung fields; there was moderate left ventricular preponderance; the transcardiac diameter was 13.7 cm., with a transthoracic diameter of 26.8 cm. Barium enema revealed diverticulosis and diverticulitis of the sigmoid colon with moderate spasm.

The admitting diagnosis was diverticulitis with a possible pelvic abscess. The possibility of an underlying carcinoma of the colon was entertained, and treatment with soft diet, antispasmodics, abdominal heat, mineral oil and Terramycin was instituted. The patient showed slight symptomatic improvement. On the third hos-

pital day she developed right lateral chest pain, pleuritic in nature, with temperature elevation to 101° F. orally, but no cough. Râles were audible in the right base, and there was a pleural friction rub. X-rays of the chest showed blunting of the right costophrenic angle, with subsequent development by the twelfth hospital day of a hazy density at the base of the right lung and minimal elevation of the right hemidiaphragm. For the next four days the patient's temperature reached a daily peak of 101° to 102° F., after which it became normal and remained normal for the rest of her hospital stay. By the eighth hospital day there was no further chest or abdominal pain. The abdomen was soft, and there was only slight tenderness in the left lower quadrant. She showed gradual improvement during the next 10 days. She had been given 500 c.c. of blood, and her hemoglobin by this time had risen to 14.6 gm. However, she continued to feel quite weak. Her nausea again became severe and she began to have emesis of almost everything she ate, although her diet was reduced to liquids and purées. Thorazine was of no benefit. The weakness became so profound that, on two occasions when she tried without assistance to reach the commode only 10 feet from her bed, she slumped to the floor and was unable to get up.

An upper gastrointestinal tract series showed no abnormality. Her blood urea nitrogen remained between 4.5 and 11 mg./100 ml. Serum sodium remained between 146 and 150 mEq./L. Serum potassium ranged from 3.7 to 4.6 mEq./L. Van den Bergh showed a direct reaction of 0.25 mg. and a total of 0.9 mg./100 ml. Thymol turbidity was 1.6 units. Cephalin flocculation was negative at 48 hours. Prothrombin time was 79%. Bromsulfalein showed 18% retention. Total protein was 5.7, with albumin 2.6 and globulin 3.1 gm./100 ml. X-ray of the chest showed complete clearing. The abdomen remained soft, with no tenderness. Physical examination remained otherwise negative, except for a persistent mild tachycardia. By the twenty-fourth hospital day it was necessary to feed her intravenously. She was extremely lethargic, sleeping most of the time, and could be awakened only briefly and with difficulty. Her weight dropped to 87 pounds. She became confused and disoriented and spoke only in a whisper.

At this point serum calcium and phosphorus determinations were done. The calcium was 14.6 mg./100 ml. and the phosphorus 2.1 mg./100 ml. Alkaline phosphatase was 5.9 S.J.R. units. Repeat determinations of calcium were 14.3 and 14.1 mg./100 ml., and phosphorus were 2.1 and 2.3 mg./100 ml. Urine calcium excretion was 439 mg./24 hours, with a volume of 2,150 c.c. A bone survey revealed only mild osteoporosis, not involving the skull and consistent with her age and postmenopausal state. Sternal marrow was normal and revealed no evidence of myeloma. Barium swallow and x-ray of thoracic inlet showed no extrinsic pressure defect on the trachea or esophagus. Normal lamina dura was present. On the thirty-seventh hospital day the neck was explored surgically. No parathyroid tissue was identified, but a nodule was palpable on the posterior surface of the right lobe of the thyroid. A right hemithyroidectomy was done and revealed a parathyroid adenoma, measuring 1 by 1 by 0.6 cm. and weighing 1.2 gm., partially embedded in the thyroid gland. Postoperatively there was prompt and striking improvement in the patient's clinical state. The mental confusion and depression disappeared, her appetite returned, and nausea lessened considerably. On the first postoperative day serum calcium was 12.8 mg./100 ml., phosphorus, 2.4/100 ml. During the next four days the calcium gradually fell to 11.8 mg./100 ml. and the phosphorus rose to 3.0 mg./100 ml. Urinary calcium excretion for the first 24 hours postoperatively was 175 mg., with a urinary volume of 1,245 c.c. This period of improvement lasted about one week, following which nausea, emesis and weakness returned, but with less intensity than preoperatively. This was accompanied by a gradual return of the calcium to 14.4 mg./100 ml. during the next 10 days. There was also hypercalciuria and hyperphosphaturia during this period. Serum phosphorus remained in the normal range. Toward the

end of this phase her clinical condition improved and all symptoms disappeared. The serum calcium gradually fell to 10.8 mg./100 ml. during the next two weeks, and the serum phosphorus stabilized at about 3.7 mg./100 ml. Urinary calcium excretion returned to normal. At this writing the patient has been at home for 10 months. She has continued to feel quite well and is able to carry on all her normal activities without difficulty. Her weight has risen to 127 pounds. Her serum calcium and phosphorus have remained normal. Renal function studies and intravenous pyelograms have shown no evidence of kidney disease.

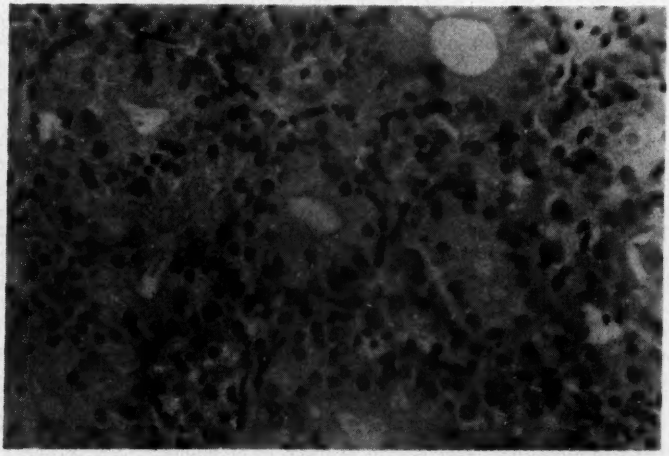

FIG. 1. Adenoma from case 1, showing slightly vacuolated cells in acinar arrangement (× 300).

Comment: The diagnosis of hyperparathyroidism in this patient was greatly obscured not only by the absence of bone or kidney disease but also by the presence of organic disease of the colon, which seemed to explain the symptoms adequately. The early course was marked by an episode of pulmonary embolism, presumably arising from a thrombosed vein associated with the pelvic infection. Suspicion of an underlying metabolic disorder was not aroused until it was apparent that her constitutional symptoms were becoming worse as her diverticulitis was clearing. The degree of inanition achieved by this patient was quite remarkable. Until the serum calcium was obtained she was thought to have an abdominal malignancy, and exploratory laparotomy was imminent. If the surgeon's hand had not been redirected from the abdomen to the neck it seems likely that she would have died quite mysteriously, with no cause of her prolonged illness and death demonstrable at autopsy. The parathyroid adenoma in all likelihood would not have been recognized for what it was, since it was embedded in the thyroid gland and histologically was almost indistinguishable from a thyroid adenoma. Black [9] has commented on this anatomic relationship, and Castleman [10, 11] has described this histologic similarity, noting that colloid material within glandular structures resembling thyroid acini may be seen within parathyroid adenomas.

This patient's postoperative course was marked by a temporary recurrence of symptoms and rise of serum calcium after an initial fall. We cannot satis-

factorily explain this phenomenon. The parallelism between the symptoms and the level of serum calcium suggests a causal relationship between the two.

Case 2. A 62 year old white male tailor was admitted to the Surgical Service at the Kaiser Foundation Hospital on August 25, 1954, for repair of a recurrent inguinal hernia. The medical history and system inventory revealed nothing of consequence. Physical findings were normal, except for the hernia and a blood pressure of 160/100 mm. of Hg. Hemoglobin was 13.0 gm.; white blood cells, 5,300, with a normal differential. The urine was clear; pH 7; specific gravity, 1.007; sugar and albumin negative; microscopic revealed a rare white blood cell per high power field. The operation was performed under spinal anesthesia without significant reduction in blood pressure. The postoperative course was uncomplicated. The patient was not catheterized. He received 2 c.c. of Combiotic twice a day prophylactically, and was discharged on August 29, 1954.

On September 8, 1954, he was admitted to the Medical Service because of progressive weakness which had begun shortly after his return home from the hospital, dysphagia, pyrosis, nausea and vomiting. He denied previous similar difficulty. His blood pressure was 100/64 mm. of Hg; heart rate, 78/minute; temperature, 98.0° F.; respiration, 20/minute. His skin was loose and dry and had poor turgor. His voice was hoarse, his tongue dry. The neck, heart and lungs were normal. The abdomen was soft and flat. There was a well healed hernioplasty scar on the right. The blood urea nitrogen was found to be 71 mg./100 ml. The urine had a specific gravity of 1.010, showed a trace of albumin, and was loaded with pus cells. No evidence of organic disease was seen on the barium swallow. It was felt that he had an exacerbation of chronic pyelonephritis with uremia, and he was given streptomycin, penicillin and intravenous fluids. Vomiting was controlled with Thorazine, 25 mg. intramuscularly twice daily. On September 16, 1954, the urine showed 10 to 15 white blood cells per high power field and no organisms. The blood urea nitrogen was 19 mg./100 ml., and the patient was no longer vomiting. He was discharged on September 21, 1954.

On October 8, 1954, he was re-admitted because of recurrence of nausea, vomiting and dehydration. He was pallid, withdrawn and lethargic. The sclerae were icteric. The urine had a specific gravity of 1.010, a trace of albumin, 50 to 60 white blood cells per high power field, and numerous hyaline and granular casts. Hemoglobin was 12 gm./100 ml.; white blood cells, 11,300/cu. mm. The blood urea nitrogen was 23 mg./100 ml. Serum sodium, chlorides, and potassium were normal. The direct van den Bergh was 1.9 mg./100 ml., with a total of 3.6 mg./100 ml. Serum amylase was 98 Somogyi units; alkaline phosphatase, 26 S.J.R. units; total protein, 6.4 gm./100 ml.; albumin, 3.2 gm./100 ml.; globulin, 3.2 gm./100 ml.; thymol turbidity, 4.5 units; creatinine, 2.9 mg./100 ml.; cephalin flocculation, negative after 48 hours. Serial liver function studies and the clinical course suggested Thorazine hepatitis as the most likely explanation for the increased serum bilirubin and alkaline phosphatase. The patient refused food from entry and had to be maintained on intravenous fluids. He showed progressive signs of inanition and wasting. Repeated upper gastrointestinal series showed no definite evidence of peptic ulcer or malignancy. Urine culture on November 4, 1954, revealed a resistant strain of Pseudomonas. He was treated with intramuscular Achromycin, with subsidence of fever. On November 18, 1954, a severe normochromic normocytic anemia was detected and he was subsequently given four units of blood. On November 27, 1954, the hemoglobin was 13.0 gm./100 ml. and the blood urea nitrogen was 27 mg./100 ml.; nevertheless, his symptoms persisted and he still refused food. On November 30, 1954, his temperature spiked to 104° F. Urine culture at this time revealed a Proteus sensitive to Furadantin. Cystoscopy showed moderate trabeculation of the bladder secondary to a median bar. Retrograde urography showed a good anatomic outline bilaterally,

with no apparent stones. On December 11, 1954, following a course of Furadantin, only occasional white blood cells were seen in the urine. The blood urea nitrogen was 20 mg./100 ml.; hemoglobin, 11.5 mg./100 ml. The apathy, nausea and vomiting persisted.

On December 12, 1954, the serum calcium was found to be 12.4 mg./100 ml.; serum phosphorus, 3.2 mg./100 ml.; total protein, 5.8 gm./100 ml.; albumin, 2.4 gm./100 ml.; globulin 3.4 gm./100 ml. Alkaline phosphatase was 7.6 S.J.R. units. Twenty-four hour urine calcium excretion was within the normal range on four occasions. A bone survey showed no evidence of skeletal decalcification. The patient was edentulous, so the absence of lamina dura was nondiagnostic. The bone marrow was normal. On January 6, 1955, the calcium was 11.6 mg./100 ml.; phosphorus, 2.9 mg./100 ml.; total protein, 5.6 gm./100 ml.; albumin, 2.5 gm./100 ml.; globulin, 3.1 gm./100 ml.; alkaline phosphatase, 6.6 S.J.R. units. On January 26, 1955, the serum calcium was 12.9 mg./100 ml. Because of the persistent hypercalcemia, exploration of the neck was advised, but the patient refused until April 6, 1955, when a parathyroid adenoma weighing 1.5 gm. was excised from the thymic fat pad of the anterior superior mediastinum. The postoperative course was smooth. By April 11, 1955, the serum calcium was 9.5 mg./100 ml., and the patient felt better. The serum calcium thereafter remained between 9.1 and 10.0 mg./100 ml. The blood urea nitrogen remained about 40 mg./100 ml.

By July he felt well enough to return to his job. Six months later he felt entirely well. His hemoglobin was 12.9 gm./100 ml., the blood urea nitrogen, 42 mg./100 ml. Serum calcium and phosphorus were normal.

Comment: This elderly patient had a prolonged illness associated with moderate obstructive uropathy, chronic pyelonephritis, and mild to moderate renal insufficiency. His course was punctuated by an episode of jaundice of the obstructive type seen with Thorazine sensitivity. However, the predominant symptoms were progressive marked weakness and wasting, and unrelenting nausea and vomiting entirely out of proportion to his renal disease. His physicians constantly harbored the impression that he had a hidden malignancy, but all efforts to demonstrate it were unrewarding. Only when the serum calcium was determined did the situation become clear.

It cannot be categorically stated that this patient had no renal complications of hyperparathyroidism. Certainly there was no radiologic evidence of renal stones or nephrocalcinosis. Nevertheless, it is possible that microscopic pyramidal calcifications contributed to his renal insufficiency. On the other hand, there was definite evidence of chronic prostatic obstruction and urinary tract infection of sufficient severity to account for the renal picture. Proteus and Pseudomonas were both cultured from the urine. In any case, we feel the point to be made here is the absence of the usual renal complications of hyperparathyroidism, i.e., demonstrable renal stones or nephrocalcinosis, which ordinarily gives rise to the first suspicion of the basic diagnosis. The presence of renal insufficiency in this patient was undoubtedly responsible for the normal serum phosphorus and the absence of hypercalciuria. We have observed normal urinary calcium excretion in one of our cases of hyperparathyroidism with renal stones and impaired renal function. The difficulty in making the correct diagnosis under these circumstances is apparent and has received attention in the literature.

The absence of bone disease in this case is also not unequivocal. Although there was no radiologic evidence of bone disease, the alkaline phosphatase was found to be elevated from October 12 to November 15, 1954. However, the

patient was jaundiced during this period, presumably from Thorazine, and the alkaline phosphatase returned to normal coincident with the subsidence of jaundice. Furthermore, the patient remained ambulatory during much of this period in spite of his weakness, and the return of the alkaline phosphatase to normal can hardly be attributed to immobilization. Finally, at no time following re-

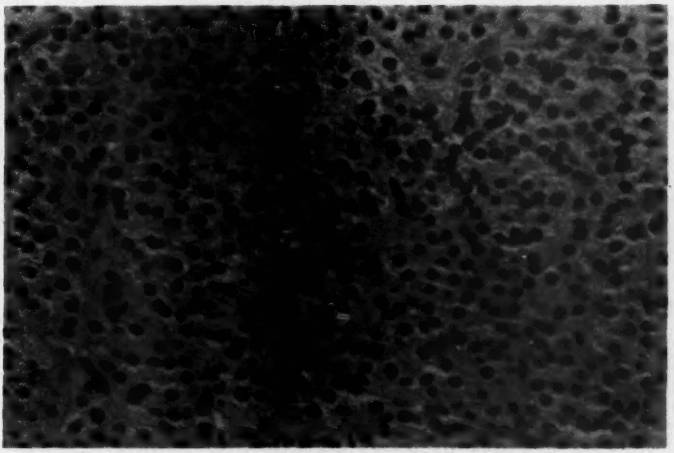

FIG. 2. Adenoma from case 2, composed of normal sized to slightly enlarged uniform chief cells (× 300).

moval of the parathyroid adenoma did the serum calcium fall below normal, nor were there any clinical signs of hypocalcemia, an unlikely circumstance in the presence of bone disease.

DISCUSSION

It should be obvious that statistics which describe hyperparathyroidism without bone or kidney disease as a rare entity are misleading. One must assume that all cases initially have neither bone nor kidney manifestations. It would seem better, therefore, to emphasize that the disease sans complications is not rare but simply rarely diagnosed. This has more than semantic significance, for it should change the attitude of the physician from one of futility to one of vigor in pursuing any clue toward the early diagnosis of the disease. This approach may save many of these people the permanent renal damage which so often has been the first clue to the diagnosis.

The diagnosis of hyperparathyroidism in the absence of kidney or bone complications is usually made accidentally, since the symptoms resulting from hypercalcemia are so common and nonspecific that the clinician's attention is rarely focused on the parathyroid glands. Symptoms such as fatigue, lassitude, myasthenia, anorexia, constipation, thirst and polyuria are usually attributed to psychoneurosis or some other entity which would rarely lead the physician to a determination of serum calcium. Once the serum calcium is obtained the diagnosis is usually apparent. Elevated serum calcium may be found in patients with metastatic malignancy of bone, multiple myeloma, sarcoidosis or the milk-alkali syndrome, or who have had prolonged immobilization. It is said to occur,

rarely, in hyperthyroidism, leukemia and polycythemia vera. The association of elevated serum calcium with a low serum phosphorus, however, occurs only (with very rare exceptions) in hyperparathyroidism or vitamin D intoxication. The differentiation between these two conditions should be simple on the basis of history alone. In the absence of renal disease the serum phosphorus is almost invariably low. In the presence of renal impairment from any cause, the serum phosphorus may be normal or elevated and the diagnosis considerably more difficult.

During a six month period at our hospital we were fortunate in finding two cases of hyperparathyroidism without bony lesions, renal stones or nephrocalcinosis. The striking features in these cases were profound weakness and persistent nausea and vomiting. In a recent paper Nielson [12] emphasized that gastrointestinal disturbances may dominate the clinical picture, with vomiting being the chief symptom. In another case he reported constipation as the most prominent feature of the disease. Several authors have noted the increased incidence of duodenal ulcer in patients with hyperparathyroidism,[8, 12] a circumstance which would vitiate the value of gastrointestinal symptoms as a clue to the unsuspected metabolic disorder. Our experience would suggest that unexplained persistent weakness, particularly in association with unexplained gastrointestinal disturbances, warrants a determination of serum calcium and phosphorus. Some patients may in this way be spared not only permanent renal damage but also, possibly, the label of psychoneurotic while the kidneys are slowly calcifying.

Goldman and Smyth [13] in 1936 and Schneider [14] in 1947 have reported cases of familial occurrence of hyperparathyroidism in a brother and sister, in cousins, in a father and daughter, and in two sisters. Nielson [12] has reported hyperparathyroidism occurring in five siblings. This may represent another avenue of approach to the early diagnosis.

Unfortunately, in most patients hypercalcemia may be attended by no symptoms, or by symptoms so insidious and mild that the patient may not seek medical aid until he has a spontaneous fracture or an episode of renal colic. Most cases of hyperparathyroidism will undoubtedly continue to be discovered by studying the calcium metabolism of all patients with renal stones, epuli, bone cysts or nephrocalcinosis. In the last 18 months three cases of hyperparathyroidism other than those reported here have been found in this hospital. One patient had renal stones, another had both stones and nephrocalcinosis, and the third nephrocalcinosis alone. In each, a parathyroid adenoma was found at operation and successfully removed.

Recently, two provocative cases have come to our attention at autopsy. In both instances there was sudden and unexpected death following a prolonged illness characterized by weakness and weight loss. One patient presented a clinical picture resembling myasthenia gravis. At autopsy a tumor was found in the anterior mediastinum which proved to be a parathyroid adenoma. The other patient died following an abdominal operation to free peritoneal adhesions. At autopsy a parathyroid adenoma was found behind the right lower pole of the thyroid gland. In each instance there was no discernible cause of death. It seems probable that these patients died of the effects of hypercalcemia, presumably a chemical death. While factual data would be difficult to obtain, it seems at least possible that acute infections or surgical procedures in patients with hyperparathyroidism may be attended by some metabolic derangement

which potentiates the hypercalcemia or its clinical effects and causes death. Both patients reported here were in apparent good health until one developed acute diverticulitis, and the other had a hernioplasty and subsequent acute urinary tract infection. For this reason it seems particularly desirable to determine the serum calcium on any patient in whom exploratory laparotomy is contemplated for vague abdominal complaints associated with a wasting and enervating illness.

Summary

Two cases of hyperparathyroidism without bone or kidney manifestations of the disease are presented.

The cardinal symptoms in each case were profound weakness, nausea, vomiting and weight loss.

It is suggested that acute infections or surgical procedures in patients with hyperparathyroidism may potentiate the hypercalcemia or its clinical effects and cause death.

Summario in Interlingua

Es presentate le casos de duo patientes con hyperparathyroidismo sin manifestationes ossee o renal. Le prime patiente esseva un femina de racia blanc de 58 annos de etate con un historia de duo menses de intermittente diarrhea, anorexia, debilitate, e perdita de peso, culminante in un breve periodo de sever dolores infero-abdominal. Diverticulitis del colon sigmoide con un sensibile massa inflammatori esseva constatate in examines physic e roentgenologic e esseva considerate como le sol causa del maladia. Post que le diverticulitis habeva essite tractate con bon successo per medio de mesuras conservatori, le persistentia del nausea, del vomito, de extreme grados de debilitate, de lethargia, e del progressive perdita de peso indicava le necessitate de cercar un altere disordine. Esseva constatate que le calcium del sero esseva elevate, durante que le phosphoro del sero esseva reducite. Hypercalciuria e hyperphosphaturia esseva demonstrate. Le phosphatase alcalin, le stato del ossos, le function renal, e le observationes pyelographic esseva normal. Le exploration chirurgic del collo resultava in le discoperta de un adenoma parathyroide includite in le lobo dextere del glandula thyroide. Le excision del adenoma resultava in le complete restablimento clinic e chimic del patiente.

Le secunde patiente esseva un masculo de racia blanc de 62 annos de etate qui disveloppava nausea, vomito, debilitate, e perdita de peso post le reparo chirurgic de un hernia inguinal. Esseva constatate que le patiente habeva moderate grados de uropathia obstructive, con infection chronic e insufficientia renal. Post que le infection e le insufficientia renal habeva essite tractate con bon successo, iste patiente continuava manifestar debilitate, apathia, nausea, vomito, e perdita de peso. Esseva trovate que le calcium del sero esseva persistentemente elevate. Le phosphoro del sero e le excretion urinari de phosphoro non esseva normal, presumibilemente a causa del insufficientia renal. Le examine del ossos monstrava nulle anormalitate. Le phosphatase alcalin esseva normal. Pyelographia produceva nulle signos de calculos o de nephrocalcinosis. Al operation, un adenoma parathyroide esseva excidite con bon successo ab le cossino de grassia thymic del mediastino antero-superior. Postea le patiente se restabliva completemente, e le calcium del sero retornava a un concentration normal.

Le aspectos cardinal in ambe casos esseva inexplicate nausea, vomito, debilitate, e perdita de peso. Ben que nonspecific, iste complexo de symptomas demanda le determination del concentrationes seral de calcium e de phosphoro, specialmente ante le effectuation de un laparotomia exploratori. Iste typo de intervention chirurgic

non produce le effecto desirate si le patiente suffre de hyperparathyroidismo. Nostre experientia suggere que in tal patientes le intervention chirurgic pote devenir le causa de un morte subitanee.

Le duo patientes del presente reporto esseva quasi moribunde quando le correcte diagnose esseva trovate. In ambe casos, un infection acute initiava un rapide progresso de debilitate in un individuo qui habeva previemente essite asymptomatic. Il pare plausibile que acute infectiones in patientes con hyperparathyroidismo es accompaniate de un certe disturbation metabolic que resulta in le potentiation del hypercalcemia o de su effectos clinic.

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EOSINOPHILIC GRANULOMA OF THE LUNG*

By Jordan Thompson, M.D., Howard A. Buechner, M.D., F.A.C.P., and Ronald Fishman, M.D., *New Orleans, Louisiana*

Since 1940, when "eosinophilic granuloma of bone" was first defined by Lichtenstein and Jaffe,[1] this disease has been reported with surprising frequency. In 1946 Dundon, Williams and Laipply[2] collected 48 cases from the literature

* Received for publication November 14, 1956.

From the Medical Service, Veterans Administration Hospital, and the Department of Medicine, The Tulane University of Louisiana School of Medicine, New Orleans, Louisiana.

Requests for reprints should be addressed to Howard A. Buechner, M.D., Chief, Medical Service, Veterans Administration Hospital, 1601 Perdido Street, New Orleans 12, Louisiana.

and added five of their own. By August, 1954, O'Neill and his co-workers [3] had brought the total number of reported cases to 189, and others have since accumulated.

Eosinophilic granuloma, as originally described, was thought to be limited to the skeletal system, but it soon became apparent that the disease was more complex than was at first supposed, since other tissues, notably skin, lymph nodes, pituitary and stomach, were not infrequently involved. In 1944 Engelbreth-Holm et al.[4] reported a case of eosinophilic granuloma of bone associated with diffuse pulmonary infiltrations, and in 1950 Adams and Kraus,[5] in describing a patient with cutaneous, renal and pulmonary lesions, offered autopsy proof for the first time of the actual existence of eosinophilic granuloma of the lung. Just one year later the rather startling report of Farinacci, Jeffrey and Lackey [6] appeared, in which they presented two cases of eosinophilic granuloma of the lung without involvement of bone or other detectable extrapulmonary lesions. Since that time three additional cases of this type have been reported.[7, 8]

In our own review of the literature we have been able to find 39 cases with pulmonary involvement.[4-35] Thirty-one of these patients had skeletal lesions as well. Three had evidence of extrapulmonary involvement, such as the pituitary gland or skin, but no lesions of bone, while, as mentioned above, only five had eosinophilic granuloma limited to the lungs alone. In 12 of the 39 cases the diagnosis was proved by lung biopsy, and in two by autopsy findings. In the remainder of the cases the diagnosis rests on biopsy of a skeletal lesion or other tissue associated with roentgenographic evidence of pulmonary involvement.

Thus, while it is now recognized that pulmonary changes are not an unusual accompaniment of eosinophilic granuloma of bone (probably occurring in about 20% of the cases), it also appears that in rare instances this disorder may be limited to the lungs alone. Whether this is the true situation, or whether lesions are also present in extrapulmonary sites but are not clinically detectable, will remain for the future to decide.

Due primarily to the work of Farber, Green and McDermott [36, 37] in this country, and Engelbreth-Holm et al.[4] in Europe, the concept has arisen that eosinophilic granuloma is intimately related to Hand-Schüller-Christian disease and Letterer-Siwe disease, and may indeed represent but a variant of the basic pathologic process common to all three disorders. While recognizing this relationship, the present authors have elected to include in the above review only those cases which have presented the specific histology of "eosinophilic granuloma."

The following report presents a sixth case of eosinophilic granuloma limited to the lungs, and the first in which prednisone therapy has been employed.

Case Report

A 42-year old Negro male janitor, employee of the Radiology Department of the Veterans Administration Hospital, New Orleans, Louisiana, was admitted to patient status on December 14, 1955, following discovery of pulmonary lesions on a routine roentgenogram of the chest. Required employment chest films had been taken semiannually for many years. On December 6, 1955, such an examination disclosed the presence of diffuse, symmetrically distributed, mottled densities throughout both lung fields (figure 1). The patient considered himself to be in excellent health and denied

respiratory symptoms of any type, although his weight had gradually declined five pounds in recent months. There was no history of exposure to silica or other respiratory irritants. In retrospect, on a previous film of June, 1955, minimal vague infiltrative lesions could be detected. All earlier chest roentgenograms were negative.

Past medical history and family history were noncontributory.

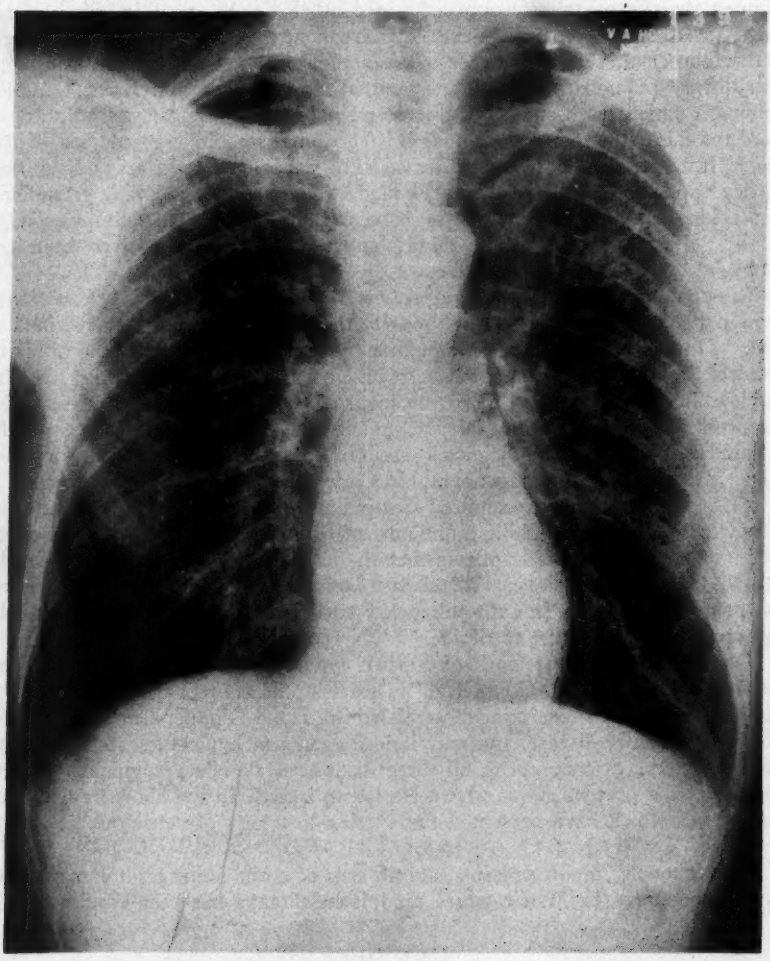

FIG. 1. Routine roentgenogram of the chest, December 6, 1955, on which date the presence of bilateral pulmonary disease was first detected.

Physical Examination: The patient was a well developed, well nourished, light-skinned Negro male who appeared to be in the best of health. The temperature was 98° F.; pulse, 76; blood pressure, 120/80 mm. of Hg. There was no lymphadenopathy. The lungs were clear. No bone tenderness or other physical abnormalities could be detected.

Roentgenograms of the chest revealed bilaterally symmetric mottled densities scattered throughout the entire extent of both lungs. Multiple small cystic areas were present within the infiltrations, suggesting a generalized "honeycomb" appearance (figures 1 and 2). Roentgenograms of the entire skeleton failed to reveal evidence of osseous pathology. A gastrointestinal series was negative.

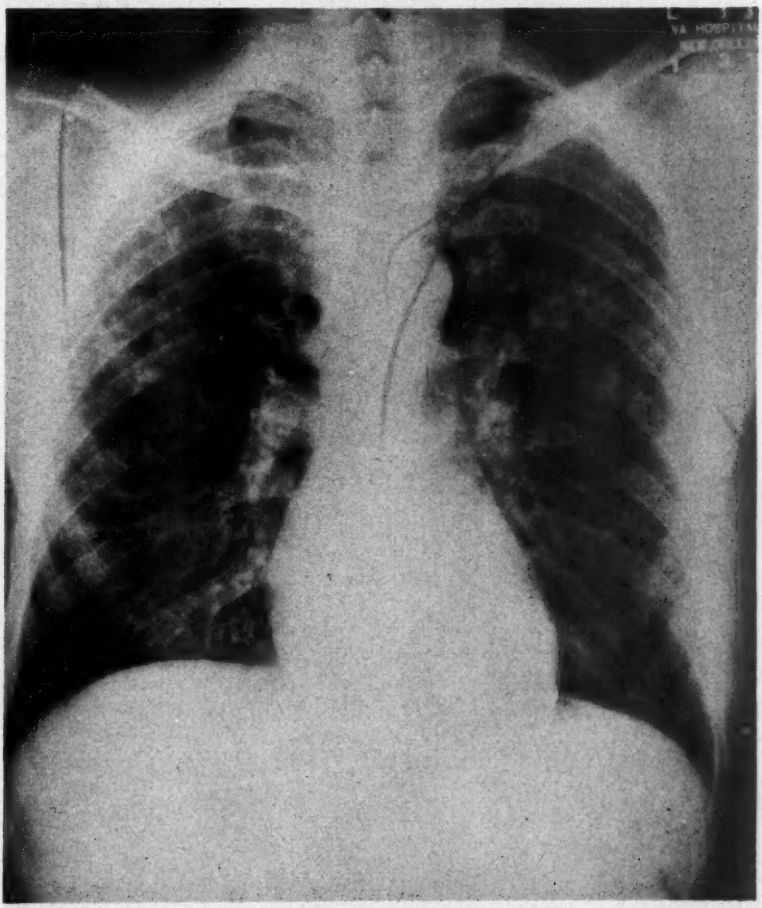

FIG. 2. Roentgenogram of chest taken six weeks after admission to the hospital, showing progression of the pulmonary lesions in spite of treatment with penicillin and tetracycline.

Laboratory Examinations: Initial hemogram: white blood cells, 5,550, with a normal differential (1% eosinophils); red blood cell count 4,770,000; hemoglobin, 14.6 gm.; hematocrit, 42; sedimentation rate, 27 mm. in one hour. Urinalysis revealed no abnormality. Sputum cultures and examinations of concentrated sputum specimens failed to detect the presence of either tubercle bacilli or pathogenic fungi. Cultures of gastric contents were also negative. The first strength tuberculin

(PPD) skin test was 3 plus. Testing with histoplasmin produced a 2 plus reaction, while the coccidioidin skin test was negative. Serum cholesterol was 170 mg.%; zinc turbidity, 14.8 units; thymol turbidity, 1.5 units; lipid turbidity, 610 mg.%; serum bilirubin, 0.75 mg.%; alkaline phosphatase, 2.5 Bodansky units; acid phos-

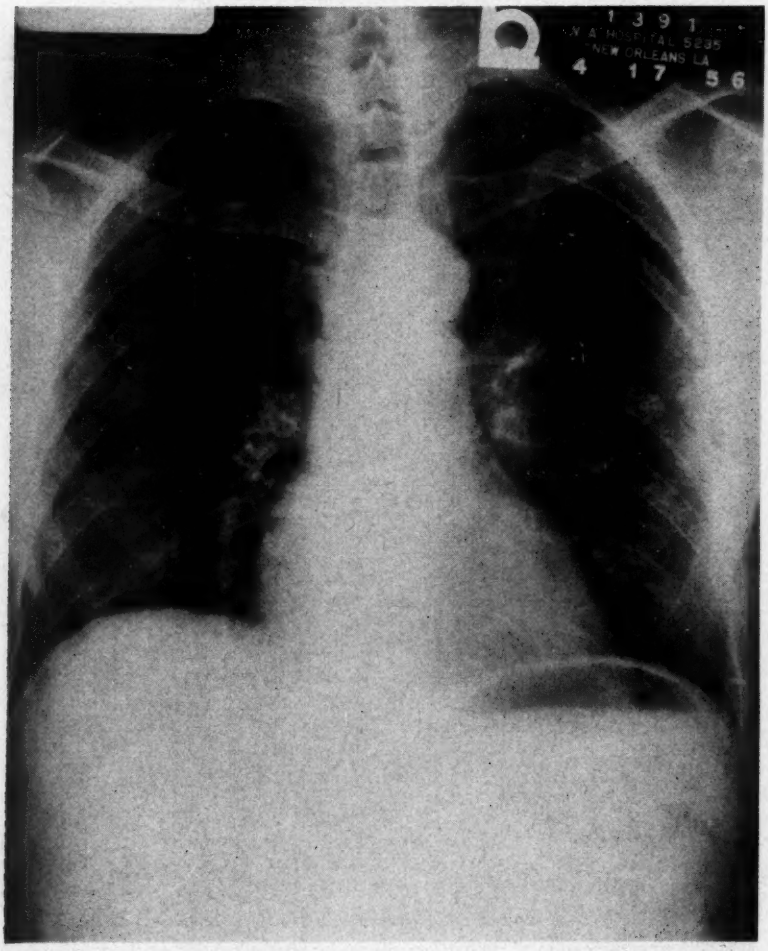

FIG. 3. Roentgenogram of the chest taken three weeks after institution of prednisone therapy, showing essentially complete clearing of the pulmonary infiltrations.

phatase, 0.75 King-Armstrong units; serum proteins, 6.50 gm.%; albumin, 4.10 gm.%; globulin, 2.40 gm.%; bromsulfalein retention, 6.91% in 45 minutes; urine urobilinogen, 0.98 Ehrlich unit; cephalin flocculation, 1 plus; serum calcium, 9.4 mg.%; inorganic phosphorus, 3.7 mg.%; serologic test for syphilis, negative. Stool examinations disclosed no abnormality. A lupus erythematosus cell preparation was negative. Study of the bone marrow revealed a very cellular reaction, with a definite

increase in plasma cells and moderate erythroid hyperplasia. No tubercle bacilli or fungi could be detected. A needle biopsy of the liver was interpreted as showing minimal histologic changes with increase in pigment (possibly lipochrome) and slight regeneration. Cultures of the liver tissue were negative. Biopsy of a scalene

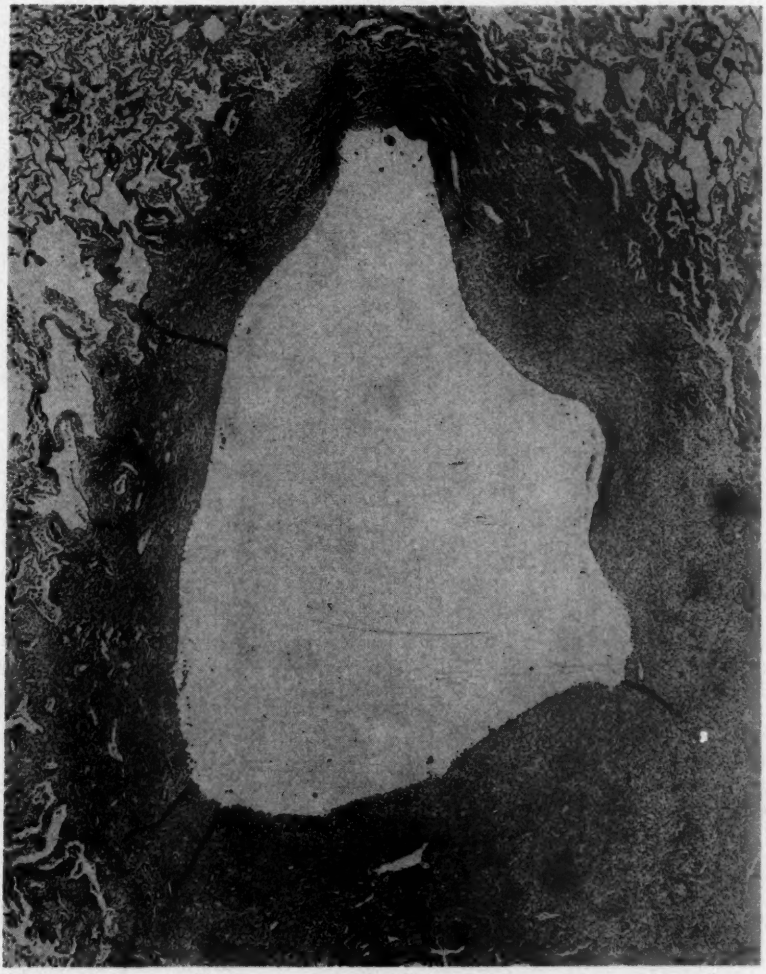

FIG. 4. Low magnification photomicrograph of the biopsy specimen, illustrating cavitation or cyst formation within the central portion of a granulomatous nodule. It is this pathologic change which undoubtedly accounts for the roentgenographic characteristic described as "honeycomb lungs."

lymph node showed only reactive hyperplasia. Cultures of this node were negative for tubercle bacilli and fungi. Bronchoscopy was unsuccessful because of poor patient coöperation. An electrocardiogram disclosed changes strongly suggestive of myocardial disease and compatible with the presence of early cor pulmonale. Studies

of pulmonary ventilation showed moderate reduction of vital capacity, while the timed vital capacity and maximal breathing capacity were within normal limits. Blood gas determinations detected mild oxygen unsaturation (92.7%). These findings were interpreted as being compatible with the presence of pulmonary fibrosis or a

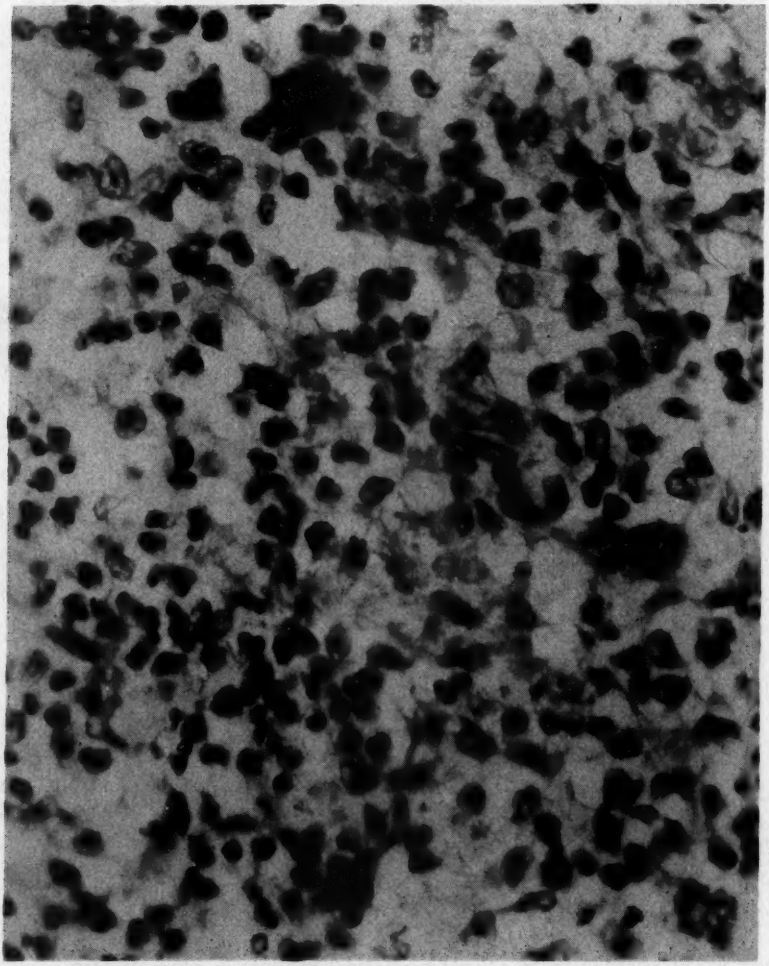

FIG. 5. High magnification photomicrograph of biopsy specimen, demonstrating characteristic histiocytic reaction heavily infiltrated with eosinophils.

diffuse granulomatous process which was producing a slight degree of impairment of oxygen diffusion at the alveolar capillary level.

Hospital Course: When initial diagnostic procedures failed to clarify the etiology of the patient's disease a course of penicillin and tetracycline was administered on an empiric basis. These medications were continued for one month. During this time

the patient remained completely asymptomatic and afebrile, but serial roentgenograms of the chest disclosed slight progression of the bilateral pulmonary lesions (figure 2). It was then decided to perform a surgical lung biopsy. Because of the presence of a strongly positive tuberculin skin test and the indeterminate nature of the pulmonary disease, the patient was placed on streptomycin and isonicotinic acid hydrazide (February 24, 1956) as a preoperative precaution. On March 5, 1956, an exploratory thoracotomy was performed. The left thorax was entered through the bed of the resected sixth rib. Numerous small nodules without any particular pattern of distribution were palpated throughout the entire lung. A few nodules presented on the surface, but most appeared to lie deeper in the lung tissue. Two of the more superficial lesions were excised from both the upper and the lower lobes. Cut section of one of the resected nodules disclosed that it contained a definite central area of cavitation or cyst formation (figure 4). Microscopic study of this tissue showed a granulomatous reaction composed of histiocytes, fibroblasts, numerous eosinophils and occasional lymphocytes and polymorphonuclear leukocytes. The eosinophils were present in sheets and small collections scattered throughout the inflammatory tissue (figure 5). The granulomatous nodule contained a large central cavity within which occasional histiocytes, lymphocytes and eosinophils were seen. At the periphery there were thickening of alveolar walls by fibrosis, and infiltration of histiocytes and eosinophils. Numerous phagocytes were seen within the alveolar spaces. Several blood vessels within the nodule and at the periphery showed marked intimal and subintimal thickening. Occasional eosinophils were present in the vessel walls. In one portion of the section a terminal bronchiole was seen in which the lining cells had proliferated and occluded the lumen. Fat stains (oil red 0) revealed occasional histiocytes filled with red-stained granules throughout the specimen. Cultures of the biopsy material were negative for acid-fast bacilli or fungi. The histologic diagnosis was eosinophilic granuloma of the lung.

The patient's postoperative course was uneventful. In an attempt to produce regression of the diffuse granulomatous process, Meticorten * was started on March 22, 1956. The patient received 30 mg. of Meticorten daily for 36 days, 20 mg. daily for the next 43 days, and 10 mg. daily for the next 42 days (until July 19, 1956). Meticorten was then withdrawn by gradual reduction in dosage, accompanied by the temporary administration of ACTH. Streptomycin and isoniazid were continued during this period to prevent possible reactivation of a dormant tuberculous focus while steroid therapy was being administered.

Response to treatment with prednisone was very gratifying. The patient immediately noted an increased sense of well-being. His appetite improved, and a subsequent weight gain of 29 pounds was observed. Serial roentgenograms of the chest disclosed rapid clearing of the pulmonary lesions. Within three weeks of the institution of steroid therapy chest films were almost within normal limits—only a few vague linear densities remained, suggestive of minimal interstitial fibrosis (figure 3). At the present time the patient is clinically well and has returned to his previous occupation. No further significant change has been observed on the most recent chest roentgenogram, taken on October 6, 1956.

Discussion

Eosinophilic granuloma of the lung is an uncommon disorder of unknown etiology and uncertain prognosis. It usually makes its appearance in the third or fourth decade of life and appears to be very rare in Negroes. Clinical characteristics of the disease are perhaps best illustrated by an analysis of the 39 cases to be found in the literature. Cough was the most frequent symptom and

* Prednisone.

was noted in 49% of the patients. When present, the cough was usually nonproductive. Weight loss, manifestations of diabetes insipidus and chest pain, which frequently presented as localized rib tenderness, each occurred in approximately 30% of the cases. Dyspnea was present in 26%. Weakness or fatigue was noted in 18%, and low grade fever in a similar number. Other, less frequent symptoms included night sweats, hemoptysis, backache, hip pain and discomfort in other skeletal areas. Spontaneous pneumothorax was observed in five patients. Over one-half of the cases had no respiratory complaints, and 18% exhibited no symptoms of any type.

An evaluation of the prognosis of eosinophilic granuloma of the lung presents a particularly baffling problem. While some authors have regarded the disease as benign in character and frequently self-limited,[7, 27] others have indicated a guarded [8] or even a grave prognosis.[38] Undoubtedly these varied opinions stem from the intimate association of this disorder with Hand-Schüller-Christian disease and Letterer-Siwe disease. Indeed, as had been previously indicated, these three conditions probably represent clinical variants of the same basic pathologic process and are thus actually inseparable. The prognosis for localized eosinophilic granuloma is the brightest, but it becomes increasingly less favorable as the characteristics of full-blown Hand-Schüller-Christian disease and Letterer-Siwe disease are approached. Thus any survey of eosinophilic granuloma will reflect a better or a poorer prognosis as it unavoidably includes more or less of the severer forms of the basic disorder. Our own analysis is, of course, subject to this same fault. Although we have scrupulously limited our study to those patients with a histologic diagnosis of eosinophilic granuloma, a number of cases presenting clinical features of Hand-Schüller-Christian disease, or even Letterer-Siwe disease, have knowingly been included. Unfortunately, the literature provides but scant long-term follow-up information. Of the 39 patients studied, no information is given as to the subsequent

TABLE 1

Results of Treatment of Eosinophilic Granuloma of the Lung Based on an Analysis of 40 Cases

	Unknown	Progressive Disease	No Change	Slight Improvement	Moderate Improvement	Marked Improvement
Irradiation	2	1	5	2	2	1
ACTH		3	3	1	1	
Cortisone		2	2		1	
Prednisone						1*
Penicillin		1*	2			
Streptomycin			1			1
Streptomycin-Isoniazid			2*			
Streptomycin-Isoniazid-PAS			1			
Tetracycline		1*				
Aureomycin			1			
Erythromycin				1		
Vitamins	1					
Urethane		1				
Resection						1
No Therapy	4	3	1		2	3

* Authors' Case.

clinical course in seven instances. Three patients exhibited progressive disease leading to early death. The remaining 29 were alive at intervals of from two and one-half months to six years after the disorder was first detected. Of this group, 16 had shown improvement or what appeared to be complete recovery, 11 were unchanged and two had progressive disease. Complete spontaneous regression of the pulmonary involvement was observed as early as six months, while in one case the pulmonary lesions persisted unchanged for as long as six years.

Treatment of eosinophilic granuloma of the lung has been highly unsatisfactory. Results are variable and inconsistent, and those patients receiving various forms of therapy appear to have fared no better than those receiving no treatment at all (table 1).

The case reported here apparently exhibited a dramatic response to prednisone; however, it is always difficult to evaluate the effects of treatment in a disease which is known to undergo spontaneous remission. Nonetheless, the authors feel that the rapid improvement which followed prednisone therapy in this case is very encouraging and definitely warrants further trial of this form of management in the future.

Summary

1. The pulmonary manifestations of eosinophilic granuloma have been recognized since 1944. Thirty-nine patients with lesions of the lungs have been reported in the literature. Of these cases, only five have had no evidence of involvement of extrapulmonary sites.

2. A sixth case of eosinophilic granuloma limited to the lungs is reported.

3. This patient is the first to receive prednisone therapy. Response to treatment was apparently highly satisfactory. The authors feel that further trial of this form of management is indicated.

Summario in Interlingua

Le manifestationes pulmonar de granuloma eosinophile es recognoscite depost 1944. Trenta-nove reportos de patientes con lesiones pulmonar se trova in le litteratura. In solmente cinque de iste casos, nulle evidentia esseva notate de affectiones in sitos extrapulmonar. Le presente reporto adde un sexte caso de granuloma eosinophile con restriction al pulmones. Isto es le prime caso in que le patiente esseva tractate con prednisona. Le responsa al tractamento pareva esser multo satisfactori, e le autores opina que essayos additional con iste forma de therapia es indicate.

Le patiente esseva un masculo negre de 42 annos de etate, empleate como portero in le Departimento de Radiologia. Le roentgenogrammas thoracic, que es un requirimento de empleo, habeva essite facite depost multe annos a intervallos de sex menses. Le 6 de decembre 1955, un de iste examines revelava le presentia de diffuse, symmetricamente distribuite e marmorate densitates in omne partes del campos de ambe pulmones. Le patiente se considerava como in stato de sanitate excellente e negava symptomas respiratori de omne genere. Le examine physic monstrava nulle anormalitate. Extense studios diagnostic—incluse roentgenogrammas del systema skeletic, un serie gastro-intestinal, numerationes sanguinee, urinanalyse, function hepatic, examines del feces, preparato de lupus erythematose, studio del medulla ossee, biopsia de nodos lymphatic, e biopsia hepatic—produceva resultatos negative o valores intra le limites normal. Le test a tuberculina (derivato proteinic purificate)

produceva un reaction de 3 plus. Tests con histoplasmina e coccidioidina esseva negative. Culturationes de sputo, contento gastric, medulla ossee, histo hepatic, e nodo lymphatic esseva negative pro bacillos tubercular e pro fungos.

Super le base de considerationes empiric, penicillina e tetracyclina esseva administrate durante un mense, sed le lesiones pulmonar manifestava leve grados de progresso. Postea un curso de streptomycina e de isoniazido esseva initiate, e un chirurgic biopsia pulmonar esseva effectuate. Le resectionate histo pulmonar contineva micre lesiones nodular con spatios cavitari o cystic al centro. Le examine microscopic establiva le diagnose de granuloma eosinophile.

A partir de iste tempore, le patiente recipeva prednisona durante un periodo de 120 dies. Ille exhibiva un immediate melioration clinic, manifeste in un altiate sensation de ben-esser, melioration del appetito, e un augmento del peso de 29 libras. Le lesiones pulmonar regredeva quasi completemente durante un periodo de tres septimanas. Le patiente ha retornate a su previe occupation e continua portar se ben al tempore de iste reporto.

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28. Henderson, L. L., and Thompson, E. C.: Corticotropin in eosinophilic granuloma, J. A. M. A. **151**: 294, 1953.
29. McKay, D. G., Street, R. B., Benirschke, K., and Duncan, C. J.: Eosinophilic granuloma of the vulva, Surg., Gynec. and Obst. **96**: 437, 1953.
30. May, I. A., Garfinkle, J. M., and Dugan, D. J.: Eosinophilic granuloma of the lung, report of three cases, Ann. Int. Med. **40**: 549, 1954.
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32. McNeil, R. S., and Cameron, H. M.: Hand-Schüller-Christian disease; report of a case with unusual lung changes, Thorax **10**: 314, 1955.
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34. Grant, L. J., and Ginsburg, J.: Eosinophilic granuloma (honeycomb lung) with diabetes insipidus, Lancet **2**: 529, 1955.
35. Mercer, W., and Duthie, R. B.: Histiocytic granulomatosis, J. Bone and Joint Surg. **38B**: 279, 1956.
36. Farber, S.: The nature of "solitary or eosinophilic granuloma" of bone, Am. J. Path. **17**: 625, 1941.
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EDITORIAL

GENETICS AND GLYCOLYSIS

It has been known for a long time that diabetes mellitus often showed a familial tendency and that to some extent this same tendency was present in other rarer melliturias. Only recently, however, have some of the genetic defects underlying the appearance of these sugars in the urine been brought to light.

Intricate and manifold in their metabolic pathways, the simple sugars of nutrition have been found to influence far more than the blood and urine sugar concentration. Clinical conditions such as cirrhosis, mental deficiency, cataract, and hemolytic anemia are now known to result, in some cases, from clearly defined defects of the carbohydrate cycle.

Carbohydrate metabolism goes through two general sequences, one independent of oxygen, called glycolytic, and one strictly dependent upon oxygen, aerobic. The glycolytic cycle is particularly interesting from a genetic standpoint, for it consists of at least two alternate parallel pathways, permitting a shunt from one to the other where a block occurs. One pathway is called the Embden-Meyerhoff sequence and was considered to be the sole route of glycolysis till a few years ago when a series of reactions was elaborated, mainly by Dickens [1, 2] in England and Horecker [3] at the National Institutes of Health. This new pathway links an enzyme studied by Warburg, glucose-6-phosphate dehydrogenase, into a loop connecting the initial steps with one of the last reactions of glycolysis. Because of this available metabolic "choice" an individual with a genetic deficiency of any one of a number of enzymes of the glycolytic cycle could survive by using the alternate pathway. This apparently is not true of the oxidative (Krebs) cycle, genetic lesions of which would probably result in an unviable fetus. Although some minimal shunts [4] have been proposed for this cycle it is unlikely that they would permit survival in the case of a major block.

One of the first known of the more subtle congenital defects of glycolysis, pentosuria,[5] actually involves the more recently discovered pathway. It was long a mystery that patients with this disease excrete large quantities of xylulose,[6] a pentose foreign to the normal diet and not found in any normal

[1] Dickens, F., and Glock, G. E.: Direct oxidation of glucose-6-phosphate, 6-phosphogluconate and pentose-5-phosphates by enzymes of animal origin, Biochem. J. **50**: 81, 1952.

[2] Dickens, F., and Williamson, D. H.: Transformation of pentose phosphates by enzymes of animal origin, Nature, London **176**: 400, 1955.

[3] Horecker, B. L., and Mehler, A. H.: Carbohydrate metabolism, Ann. Rev. Biochem. **24**: 207, 1955.

[4a] Bessman, S. P.: Relation of glutamic acid metabolism to certain members of the Krebs cycle in brain, II Congrès Int. de Biochimie, Res. Des. Comm. 31, 1952.

[4b] Layne, E. C., and Bessman, S. P.: Effect of glutamate on coupled phosphorylation in brain, Federation Proc. **15**: 968, 1956.

[5] Salkowski, E.: Über das Vorkommen von Pentosen im Harn, Ztschr. f. physiol. Chem. **27**: 507, 1899.

[6] Enklewitz, M., and Lasker, M.: Origin of l-xyloketose (urine pentose), J. Biol. Chem. **110**: 443, 1935.

body fluid except in trace quantities.[7] Its formation and metabolism were studied extensively by Touster's group.[7,8] Pentosuria, however, is not usually associated with clinical symptoms—other than irritation with insurance examiners—and may pass as a curiosity to the practitioner, albeit a mine of information for the scientist.

Galactosemia is of much more serious import. Recognized as a clinical entity 40 years ago[9] it had been studied intermittently for the past decade.[10-12] The discovery of a lesion in the secondary utilization of galactose demonstrable in red blood cells by Schwarz[13] in England, opened the way to an understanding of the disease. The enzyme lesion was rapidly elucidated by Kalckar,[14] who devised a test for the specific reactions in red cells. Sidbury[15] has proposed a mechanism whereby most of the symptoms of galactosemia can be explained. Shortly after birth the infant with the full blown disease develops jaundice, ascites and cataracts. The blood "sugar" is elevated, particularly after a milk feeding, and there is "sugar" in the urine. This reducing sugar can be shown to be galactose, and, indeed, there is usually normal or even low blood glucose, to which the mental deficiency usually seen in the untreated case has been attributed.[10] Removal of all substances which could supply galactose from the diet, including milk, milk sugar, and synthetic nutrients contaminated with lactose results in marked improvement and frequently a completely normal child. The cataracts regress, the jaundice disappears and the child grows mentally as well as physically. The lesion remains, however, and manifests itself throughout life by a markedly abnormal galactose tolerance curve. As the untreated child grows older, his normal diet gradually includes less and less milk, and the galactose disappears from blood and urine, making diagnosis difficult. This tardy remission of symptoms can result in physically normal but mentally defective adults. Such a case has been studied by Anderson,

[7] Touster, O., Hutcheson, R. M., and Rice, L.: Influence of d-glucuronolactone on excretion of l-xylulose by humans and guinea pigs, J. Biol. Chem. **215**: 677, 1955.

[8] Hollmann, S., and Touster, O.: Enzymatic pathway from l-xylulose to d-xylulose, J. Am. Chem. Soc. **78**: 3544, 1956.

[9] Goppert, F.: Galactosurie nach milch Zucker, zugabe bei Angeborenen familiaren chronischen Leberleiden, Berl. klin. Wchnschr. **54**: 473, 1917.

[10] Mason, N. H., and Turner, M. E.: Chronic galactemia, Am. J. Dis. Child. **50**: 359, 1935.

[11] Brock, E., and Rapoport, B.: Galactosemia in an infant with cataracts, Am. J. Dis. Child. **70**: 267, 1945.

[12] Darby, W. J., and Day, P. L.: Blood sugar levels in rats receiving the cataractogenic sugars, galactose and xylose, J. Biol. Chem. **132**: 503, 1940.

[13] Schwarz, V., Goldberg, L., Komrower, G. M., and Holzer, A.: Metabolic observations on the erythrocytes from cases of galactosemia, Biochem. J. **62**: 34, 1955.

[14a] Kalckar, H. M., Anderson, E. P., and Isselbacher, K. J.: The enzyme lesion in galactosemia, Proc. Nat. Acad. Sc. U. S. **42**: 49, 1956.

[14b] Kalckar, H. M., Anderson, E. P., and Isselbacher, K. J.: Galactosemia, a congenital defect in a nucleotide transferase, Biochim. et. Biophys. Acta **20**: 262, 1956.

[15a] Sidbury, J. B., Jr.: The enzymatic lesion in galactosemia, J. Clin. Investigation **36**: 929, 1957.

[15b] Sidbury, J. B., Jr.: Galactose-1-phosphate inhibition of the phosphoglucomutase, Abstr. Am. Chem. Soc. meeting, Sept. 1957.

Kalckar and Isselbacher [16] at the National Institutes of Health. Galactose intolerance cannot be used diagnostically in adults, since liver disease, which is part of the syndrome itself, causes an abnormal galactose tolerance. Nevertheless galactosemia persisting into adulthood might well be a factor in the etiology of some cases of cirrhosis, and of mental retardation, and should be considered, particularly if there is some familial history of childhood abnormality.

The glycolytic pathways leading directly from glycogen can be altered genetically in one of three ways, all of which result in a clinical syndrome in children of hepatomegaly, failure to thrive, occasional hypoglycemia and ketosis, and frequently cirrhosis. The unifying phenomenon common to this group of three lesions is that all cause more or less excessive storage of glycogen in the liver.[17] This has given them the name glycogen storage or Von Gierke's disease. The late Gerti Cori's elegant researches into the enzymology of this syndrome led to its separation into the three enzymatic types. One type, the most common, frequently develops hypoglycemia, since the major source of blood sugar, the glucose-6-phosphatase reaction, is missing or severely attenuated in these patients.[18] Starvation type ketosis and hypoglycemic convulsions occur most readily in these children. In the two other types the enzymes which are responsible for the branched structure of glycogen are defective or absent,[19, 20] leading to bizarre configurations of glycogen which seem to act as foreign bodies causing early cirrhosis in addition to glycogen storage. The occurrence of the disease suggests a hereditary transmission, and the fact that many cases reach adulthood (or disappear from the observation of pediatricians) leads to the suspicion that a number of milder cases may turn up as liver disease in adults, possibly exacerbated by infectious hepatitis. Here again a history of childhood disorders, or of disease in the children of siblings might reveal clues valuable to the diagnosis and treatment of adult disease.

The rapidly unfolding story of hemolytic syndromes and their relation to glycolysis provides another example of the genetic role of this phase of carbohydrate metabolism. Studies in Altman's laboratory [21, 22] demonstrated a defective red cell glycolysis in hereditary spherocytosis and this initiated an extensive investigation of the red cell enzymes in hemolytic disease.

[16] Anderson, E. P., Kalckar, H. M., and Isselbacher, K. J.: Defect in uptake of galactose-1-phosphate into liver nucleotides in congenital galactosemia, Science **125**: 113, 1957.

[17] Von Gierke, E.: Hepato-nephromegalia glykogenica (Glykogenspecherkrankheit der Leber und Nieren), Beitr. z. path. Anat. u. z. allg. Path. **82**: 497, 1929.

[18] Cori, G. T., and Cori, C. F.: Glucose-6-phosphatase of the liver in glycogen storage disease, J. Biol. Chem. **199**: 661, 1952.

[19] Illingworth, B., and Cori, G. T.: Structure of glycogens and amylopectins. III. Normal and abnormal human glycogens, J. Biol. Chem. **199**: 653, 1952.

[20] Illingworth, B., Cori, G. T., and Cori, C. F.: Amylo-1,6 glucosidase in muscle tissue in generalized glycogen storage disease, J. Biol. Chem. **218**: 123, 1955.

[21] Prankferd, T. A. J., Altman, K. I., and Young, L. E.: Abnormalities of carbohydrate metabolism of red cells in hereditary spherocytosis, J. Clin. Investigation **33**: 957, 1954.

[22] Prankferd, T. A. J., Altman, K., and Young, L. E.: Abnormalities of carbohydrate metabolism of red cells in hereditary spherocytosis, J. Clin. Investigation **34**: 1268, 1955.

Subsequently the Chicago group [23] showed a clear enzyme deficit in patients with a hemolytic idiosyncrasy to primaquine, a reaction observed to occur on a genetic basis in Negroes.[24] The circuitous route by which primaquine toxicity manifests itself has been further revealed by the finding that the enzymatic defect responsible for the toxicity is not related at all to the drug. Apparently the missing enzyme, glucose-6-phosphate dehydrogenase, Warburg's "Zwischenferment," is responsible for the maintenance of the reduced glutathione content of the red cell. When the glutathione is oxidized it is unable to "protect" the red cell against any hemolytic agent. This phenomenon was studied by Marks, Gross, and Childs,[25] resulting in an elucidation of the peculiar phenomenon that naphthalene and phenylhydrazine are toxic in a hemolytic manner only to some individuals. Now it is clear that sensitivity to these hemolytic agents is a hereditary trait transmitted as a sex-linked gene of intermediate dominance. Zinkham has shown the same hereditary defect to be operative in favism.[26]

There may be more to this than the esoteric drug reaction, however. It has been shown by Gurin [27] and by Bucher [28] that cholesterol and fat are dependent upon glycolysis for their synthesis; Chaikoff [29] reported that the peculiar derangement of lipid metabolism in diabetes in which cholesterol is synthesized and fat is not can be reversed by insulin or by increased glycolysis. The dependence of fat synthesis upon the hydrogen generated by glucose-6-phosphate dehydrogenase has been documented by Langdon [30] and by Siperstein.[31] The circle comes round to probably the most studied and most mysterious of metabolic diseases, diabetes.

To date the enzymatic mechanism of diabetes is obscure, and the current

[23] Carson, P. E., Flanagan, C. L., Lakes, C. E., and Alving, A. S.: Enzymatic deficiency in primaquine sensitive erythrocytes, Science **124**: 484, 1956.

[24] Hockwald, R. S., Arnold, J., and Clayman, C. B.: Toxicity of primaquine in Negroes, J. A. M. A. **149**: 1568, 1952.

[25a] Marks, P.: Studies on the mechanism of aging of red cells with particular reference to alterations in carbohydrate metabolism, Conference on Enzymes in Blood, The New York Academy of Sciences Section of Biology, Feb. 26–27, 1958.

[25b] Gross, R. T.: Hereditary enzymatic defect in red blood cells: Its relation to certain drug-induced hemolytic anemias, Conference on Enzymes in Blood, The New York Academy of Sciences Section of Biology, Feb. 26–27, 1958.

[25c] Childs, B., Zinkham, W. H., Browne, E. A., Kimbro, E. L., and Torbert, J. V.: A genetic study of a defect in glutathione metabolism of the erythrocyte, Bull. Johns Hopkins Hospital **102**: 21, 1957.

[26] Zinkham, W. H., Lenhard, R. E., and Childs, B.: A deficiency of glucose-6-phosphate dehydrogenase activity in the red cells from patients with favism, Bull. Johns Hopkins Hospital, in press.

[27] Dituri, F., and Gurin, S.: Fat synthesis in cell free extracts, Arch. Biochem. and Biophys. **43**: 231, 1953.

[28] Bucher, N. L. R., Grover, J. W., and Kingston, R.: Incorporation of C^{14} from acetate into cholesterol by liver cell fractions, Federation Proc. **13**: 19, 1954.

[29a] Chernick, S. S., and Chaikoff, I. L.: Two blocks in carbohydrate utilization in the liver of the diabetic rat, J. Biol. Chem. **188**: 385, 1951.

[29b] Hotta, S., and Chaikoff, I. L.: Cholesterol synthesis from acetate in the diabetic liver, J. Biol. Chem. **198**: 895, 1952.

[30] Langdon, R. G.: The biosynthesis of fatty acids in rat liver, J. Biol. Chem. **226**: 615, 1957.

[31] Siperstein, M. D., and Fagan, V. M.: Role of glycolysis in fatty acid and cholesterol synthesis in normal and diabetic rats, Science **126**: 1012, 1957.

theory rejects enzymes and bases the action of insulin on membrane permeability.[32] A role of insulin as an integrator of glycolysis and oxidative metabolism has been proposed.[33]

In addition to its metabolic complexities, diabetes enjoys a peculiar position among genetically determined diseases. Empirically it is quite clear that there is a tremendous hereditary factor in diabetes, and that it is, in all probability, genetically determined. This having been considered, we are faced with the fact that the genetic transmission of diabetes cannot be explained completely using the knowledge available.[34, 35] Why the disease occurs at different times in life, its peculiar variability and its association with degenerative phenomena are at present unexplainable. The most likely possibility is that, as in the case of glycogen storage disease, there is a group of diseases which cannot be differentiated because the enzyme lesions are as yet unknown. When the metabolic abnormalities are unravelled we can expect to see some order in this chaos.

The family history bids fair to become not a minor portion of the clinical anamnesis, but perhaps will play a major role in diagnosis in the near future. The most difficult steps have been taken and the way has been clearly indicated. This patchwork of heredity, with its accretions and losses represents an ever changing but ever constant template upon which the form and substance of the human being are molded. As the tentmaker has written

> "With earth's first clay they did the last man's knead,
> And then of the last harvest sowed the seed.
> Yea the first morning of creation wrote
> What the last dawn of reckoning shall read."

S. P. BESSMAN, M.D.

[32] Levine, R., Goldstein, M., Klein, S., and Huddlestun, B.: The action of insulin on the distribution of galactose in eviscerated nephrectomized dogs, J. Biol. Chem. **179**: 985, 1949.

[33] Bessman, S. P.: A contribution to the mechanism of diabetes mellitus, *in* Fat Metabolism, edited by V. A. Najjar, Johns Hopkins Press, 1954.

[34] Harris, H.: The familial distribution of diabetes mellitus. A survey of the relatives of 1241 diabetic propositi, Ann. Hum. Gen. **15**: 95, 1950.

[35] Steinberg, A. G., and Wilder, R. M.: A study of the genetics of diabetes mellitus, Am. J. Hum. Gen. **4**: 113, 1952.

REVIEWS

Principles of Clinical Electrocardiography. By MERVIN J. GOLDMAN, M.D. 310 pages; 25.5 × 17.5 cm. (paper-bound). Lange Medical Publications, Los Altos, Calif. 1956. Price, $4.50.

The Lange Medical Publications who have published similar Handbooks and Reviews have presented here for Dr. Goldman, Assistant Chief of the Medical Service and Cardiologist for the Oakland Veterans Administration Hospital and Assistant Clinical Professor of Medicine of the University of California School of Medicine at San Francisco, a manual of electrophysiological concepts as applied to electrocardiography with graphic illustrations of principles and clinical examples of each. The author surpasses his goals of reviewing elementary electrocardiography. The simplification of theory and its graphic representation makes apparent at once what is sometimes lost in lengthy discussion. The discussion of leads systems and their inter-relationships is a welcome addition to a work of this type. Nomenclature and criteria are included for the normal as well as the various pathologic entities discussed. The influence of age, positions of heart and various physiologic and drug induced changes as well as of electrolyte disturbances are discussed. The auricular arrhythmias are presented from a unitarian concept. While this is not universally accepted, it serves as a good teaching device for clinical electrocardiography. The ventricular arrhythmias also lend themselves well to this type of diagrammatic illustration. The student of electrocardiography will find this a valuable addition to his texts.

A more permanent type of binding seems warranted.

A. D. R.

Cardiovascular Rehabilitation. Edited by PAUL DUDLEY WHITE, M.D., HOWARD A. RUSK, M.D., BRYAN WILLIAMS, M.D., and PHILIP R. LEE, M.D. 155 pages; 21 × 14 cm. The Blakiston Division, McGraw-Hill Book Co., Inc., New York. 1957. Price, $6.50.

In 1920 the Federal government, realizing a need for returning the disabled to productive employment, established the Vocational Rehabilitation Program. In 1941 the New York Heart Association established the first cardiac work classification unit in response to a demand by the New York State Employment Agency for a description of the functional capacity of cardiacs. Since then, 40 such units serving 2,000 patients have been established in the United States. These are oriented not only as a community service program, but also incorporate basic technics in examining the cardiac-pulmonary response to the stress of work. Since 1941 a small group of physicians and their staffs have directed their attention to the paramount problem of returning the cardiac to his job. This book is an edited summary of a conference held by these men in 1956. Expressed are their experiences, successes and failures, regarding the problem in management and rehabilitation of the cardiovascular patient. Presented were the major problems facing the practicing physician; areas of current future research; requirements in the education of physicians and the public for a more constructive approach to cardiovascular rehabilitation.

This book should be required reading for students, medical educators and physicians responsible for the care and employment of cardiac patients. For the specialist

already aware of this urgent problem, it will serve as a prologue to the awaited transactions of the Wisconsin Conference on work and the heart now in publication.

Current cardiovascular morbidity suggests that this volume be studied by those concerned with the cardiac patient.

F. B.

Virus Diseases and the Cardiovascular System: A Survey. By ERNEST LYON, M.D. 215 pages; 22.5 × 14 cm. Grune & Stratton, New York. 1956. Price, $5.75.

This volume is an excellent review for all physicians interested in the relationship of viral agents and the cardiovascular system. Dr. Lyon presents his data in a very readable and authoritative manner.

The book is arranged conveniently in three parts: (1) general remarks and cardiovascular concepts dealing with pathogenesis and pathologic physiology; (2) the cardiovascular manifestations of specific viral infections, and (3) cardiovascular manifestations of the rickettsias. Each specific virus infection is defined clearly with concise description of the disease and the pertinent clinical manifestations. Each virus disease is discussed thoroughly from the cardiovascular viewpoint. The book is up-to-date (with certain minor exceptions), and proper emphasis is placed on the role of viruses as a cause of myocarditis. The peripheral vascular system is given equal coverage. Specific and general therapeutic considerations are presented in all sections where applicable.

The bibliography for each section is sufficiently complete to provide valuable references for the internist, pathologist and virologist.

T. E. WOODWARD, M.D.

Tumors of the Pituitary Gland and Infundibulum (Atlas of Tumor Pathology, Section X, Fascicle 36). By JAMES W. KERNOHAN, M.D., and GEORGE P. SAYRE, M.D. 81 pages; 26 × 20 cm. (paper-bound). Published by the Armed Forces Institute of Pathology under the Auspices of the Subcommittee on Oncology of the Committee on Pathology of the Division of Medical Sciences of the National Academy of Sciences—National Research Council. 1956. Price, $1.00.

This fascicle of the *Atlas of Tumor Pathology* offers a sound summary of present knowledge concerning the pathology of pituitary gland tumors. The relative frequency of these tumors is stressed.

A review of the gross and microscopic anatomy orients the reader for the ensuing pathological study. Case histories document typical clinical experiences. The photographic plates are technically superior. Free use of synonyms facilitates the use of the text by those accustomed to varied terminologies.

This publication will be a useful reference for pathologists, neurologists and neurosurgeons.

J. O. S.

The Queen Charlotte's Text-Book of Obstetrics. By fifteen authors. 547 pages; 24 × 15.5 cm. J. & A. Churchill Limited, London; distributed by Little, Brown & Company, Boston. 1957. Price, $11.50.

The oldest lying-in hospital in the British Isles is the Queen Charlotte. It has had an illustrious history, due to the high standards of its faculty. In 1927 the first edition of the text book appeared; and every three to four years since, except during the immediate post-war period, it has been revised.

The present revision deals with the practice of obstetrics as taught by fifteen of its faculty. Herein lies its value as well as its faults. In the preface it is stated that "Little space has been given to untried methods or purely theoretical matters." Unfortunately, alternative tried methods of therapy in the various obstetrical problems are frequently omitted. In this respect the treatise is didactic with personalized opinions predominating.

The volume furnishes sound guidance in the practice of obstetrics. For the well trained obstetrician it offers in many instances a different viewpoint and philosophy.

D. F. K.

Klinische Physiologie und Pathologie. By Prof. Dr. FERDINAND HOFF. 1120 pages; 25 × 17.5 cm. Georg Thieme Verlag, Stuttgart; in the U. S. A. and Canada: Intercontinental Medical Book Corporation, New York. 1956. Price, $18.95.

In its fifth edition, this outstanding book has been greatly expanded and revised. Professor Hoff has called in collaborating authors in some of the special fields of internal medicine. Hematology, endocrinology and metabolism are dealt with in more detail.

Of especial interest is the attempt to break away from the concept of localized pathology in favor of a broad understanding of a disease process involving the organism as a whole (Ganzheitsmedizin). A valuable chapter is that entitled Steuerungseinrichtigungen (i.e., Mechanisms of Regulation).

The book is up-to-date. The adequate bibliography shows that foreign publications were incorporated. The point of view is stimulating and the clinical features instructive. It will be helpful to both undergraduate and graduate students.

A. S.

BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

Aortography: Its Application in Urological and Some Other Conditions. By W. BARR STIRLING, CH.M., F.R.C.S. (Ed.), F.R.F.P.S.G., Senior Assistant, Urological Department, Glasgow Royal Infirmary, etc. 292 pages; 25.5 × 17.5 cm. 1957. The Williams & Wilkins Company, Baltimore. Price, $10.00.

Chemotherapy and Chemoprophylaxis in Tuberculosis Control: Report of a Study Group. World Health Organization Technical Report Series No. 141. 12 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

The Clinical Application of Hormone Assay. By JOHN A. LORAINE, M.B., Ph.D. (Ed.), M.R.C.P. (Ed.), Member of Scientific Staff, Clinical Endocrinology Research Unit, Medical Research Council, University of Edinburgh, etc.; with a foreword by J. H. GADDUM, ScD., F.R.S., Professor of Pharmacology and

Materia Medica, University of Edinburgh. 368 pages; 22.5 × 14.5 cm. 1958. The Williams & Wilkins Company, Baltimore. Price, $7.00.

Conference on Public Health Training of General Practitioners, Geneva, 29 October–2 November 1956: Report. World Health Organization Technical Report Series No. 140. 21 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Diabetes as a Way of Life. By T. S. DANOWSKI, M.D., Renziehausen Professor of Research Medicine, University of Pittsburgh School of Medicine, etc. 177 pages; 19.5 × 13 cm. 1957. Coward-McCann, Inc., New York. Price, $3.50.

The Early Diagnosis of the Acute Abdomen. 11th Ed. By SIR ZACHARY COPE, B.A., M.D., M.S. Lond., F.R.C.S. Eng., Consulting Surgeon, St. Mary's Hospital, Paddington. 188 pages; 22.5 × 14.5 cm. 1957. Oxford University Press, New York. Price, $4.50.

Erythroblastosis Fetalis, Including Exchange Transfusion Technic. New England Journal of Medicine *Medical Progress Series.* By FRED H. ALLEN, JR., M.D., Clinical Associate in Pediatrics, Harvard Medical School, etc.; and LOUIS K. DIAMOND, M.D., Associate Professor of Pediatrics, Harvard Medical School, etc. 143 pages; 19.5 × 12.5 cm. 1958. Little, Brown and Company, Boston. Price, $4.00.

Expert Committee on Health Statistics: Fifth Report. World Health Organization Technical Report Series No. 133. 22 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Expert Committee on Yellow Fever Vaccine: First Report. World Health Organization Technical Report Series No. 136. 21 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

La Fonction Endocrine du Testicule: Physiologie, Explorations, Pathologie, Thérapeutique. Colloque sur la Fonction Endocrine du Testicule (Paris—Juillet 1957). Organisé par la Société Nationale pour l'Étude de la Stérilité et de la Fécondité. Secrétaire général du colloque: Pr. agr. GILBERT DREYFUS. 532 pages; 25.5 × 16.5 cm. (paper-bound). 1957. Masson & Cie., Paris. Price, 4.500 fr.

Heart Disease and Pregnancy: Physiology and Management. By C. SIDNEY BURWELL, M.D., Samuel A. Levine Professor of Medicine, Harvard University, etc.; and JAMES METCALFE, M.D., Associate in Medicine, Harvard University, etc. 338 pages; 24.5 × 16 cm. 1958. Little, Brown and Company, Boston. Price, $10.00.

Heart Disease—Cause, Prevention, and Recovery. By PHILIP S. CHEN, Ph.D., Professor of Chemistry and Chairman of Division of Natural Sciences, Atlantic Union College; with the assistance on Part I of PHILIP S. CHEN, JR., Ph.D., National Heart Institute. 189 pages; 21 × 14 cm. 1958. The Chemical Elements, South Lancaster, Massachusetts. Price, $3.00.

Joint ILO/WHO Committee on Occupational Health: Third Report. World Health Organization Technical Report Series No. 135. 22 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Malaria Conference for the Eastern Mediterranean and European Regions, Athens, Greece, 11–19 June 1956: Report. World Health Organization Technical Report Series No. 132. 47 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Measurement of Levels of Health: Report of a Study Group. World Health Organization Technical Report Series No. 137. 29 pages; 24 × 16 cm. (paper-bound). 1957. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Medical Specialization: A Survey of Existing Legislation. 39 pages; 24 × 16 cm. (paper-bound). 1958. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.

Methods in Medical Research. Vol. 7. JAMES V. WARREN, Editor-in-Chief. Governing Board: IRVINE H. PAGE, Chairman; RENÉ J. DUBOS, C. N. H. LONG, CARL F. SCHMIDT and DAVID L. THOMSON. 237 pages; 22.5 × 14 cm. 1958. The Year Book Publishers, Inc., Chicago. Price, $7.50.

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